Κληρονομικές διαταραχές αρτηριακής υπέρτασης

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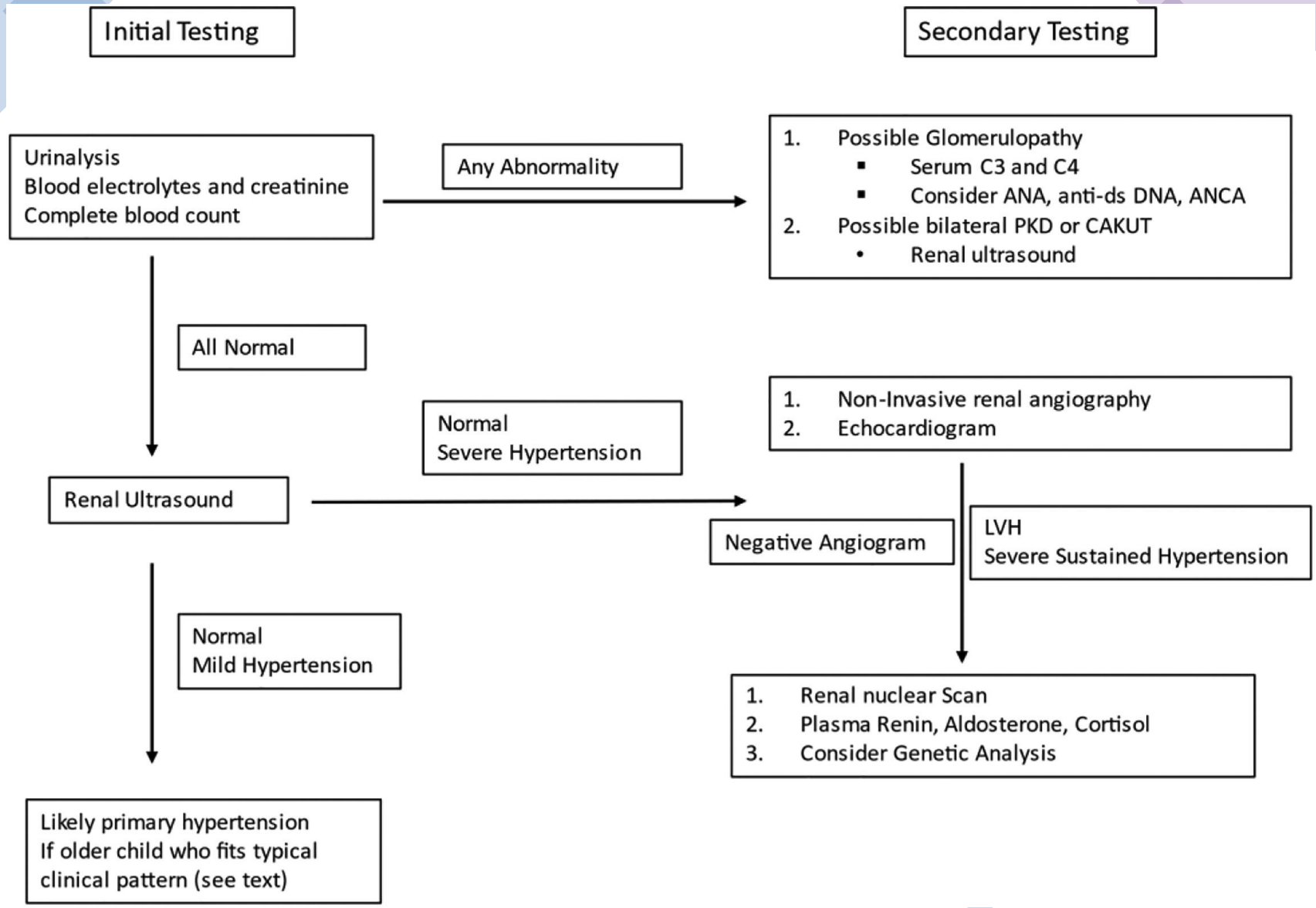
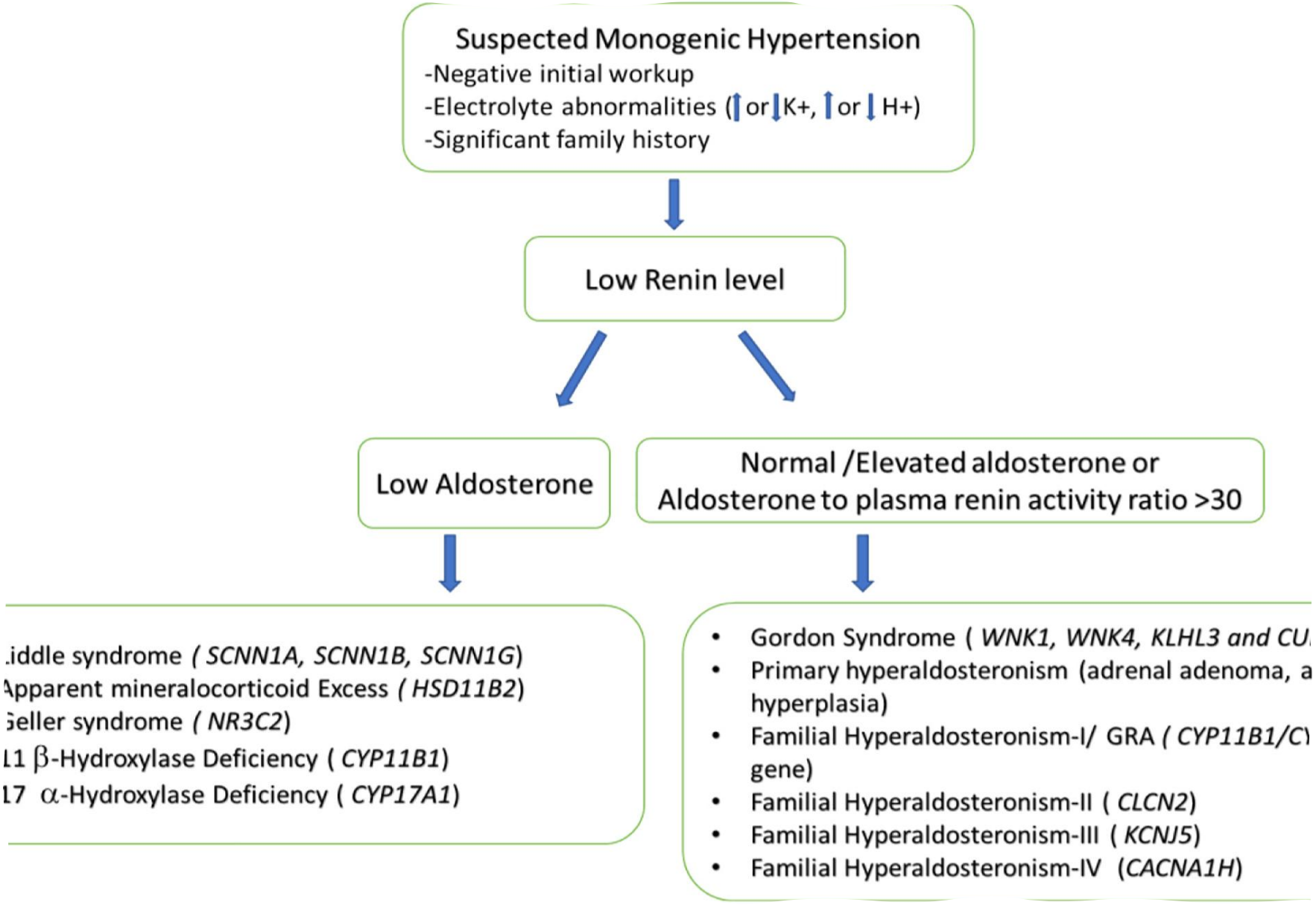
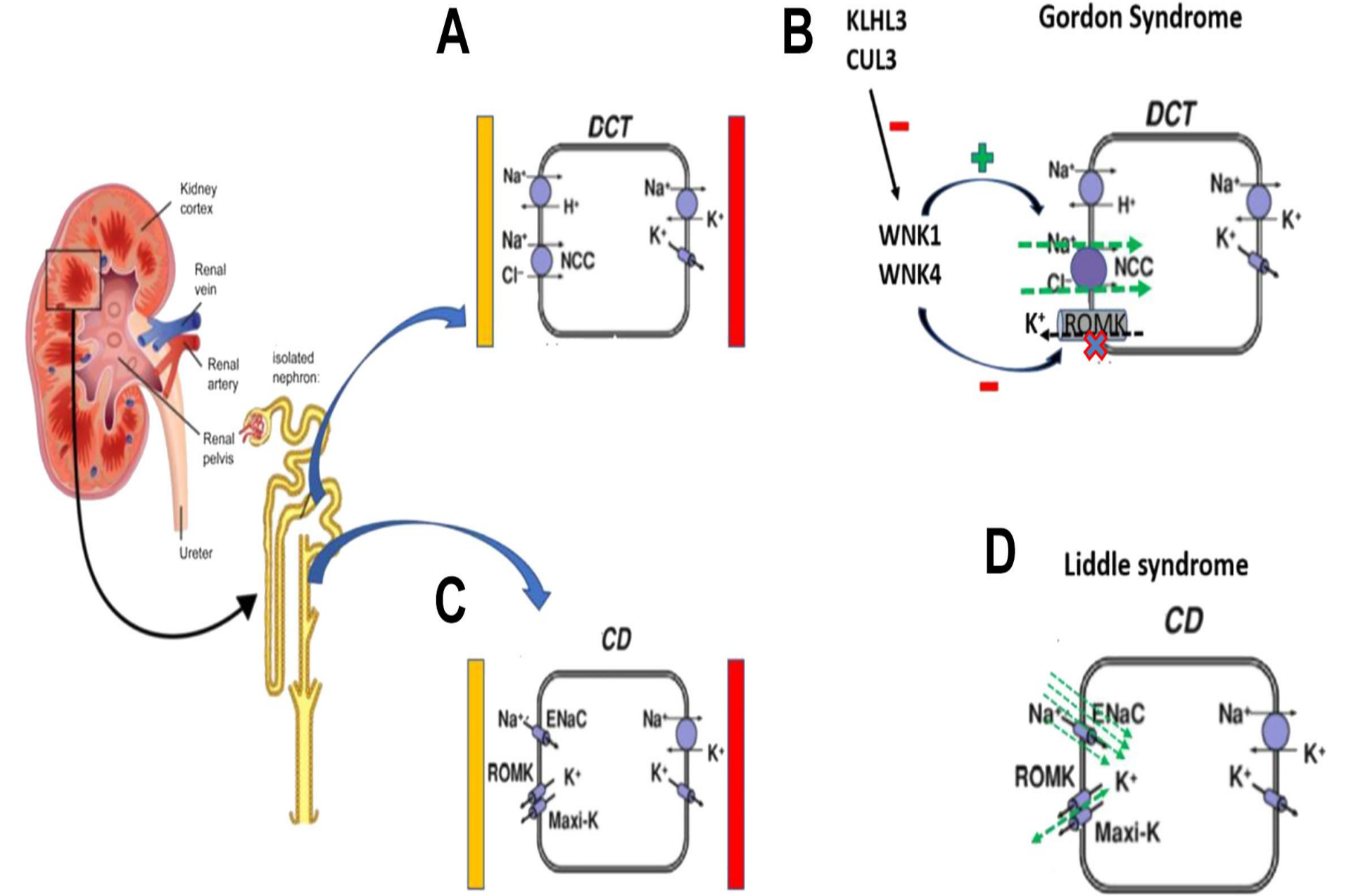
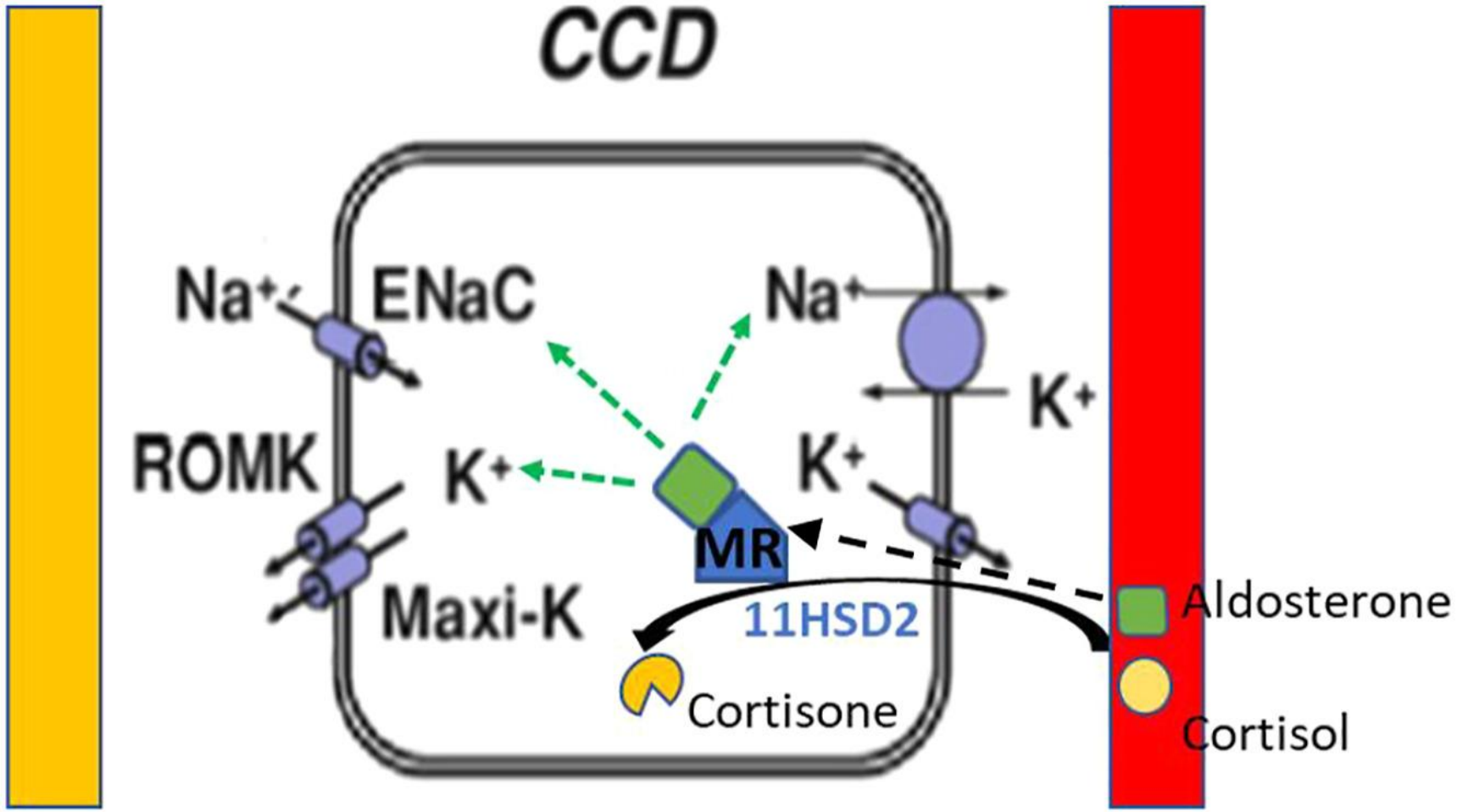
Πρόεδρος Επιστ. Συμβουλίου ΕΛΠΕΝ & Δ/ντής Κλιν. Γενετικής Νοσ/μείου Ντυνάν

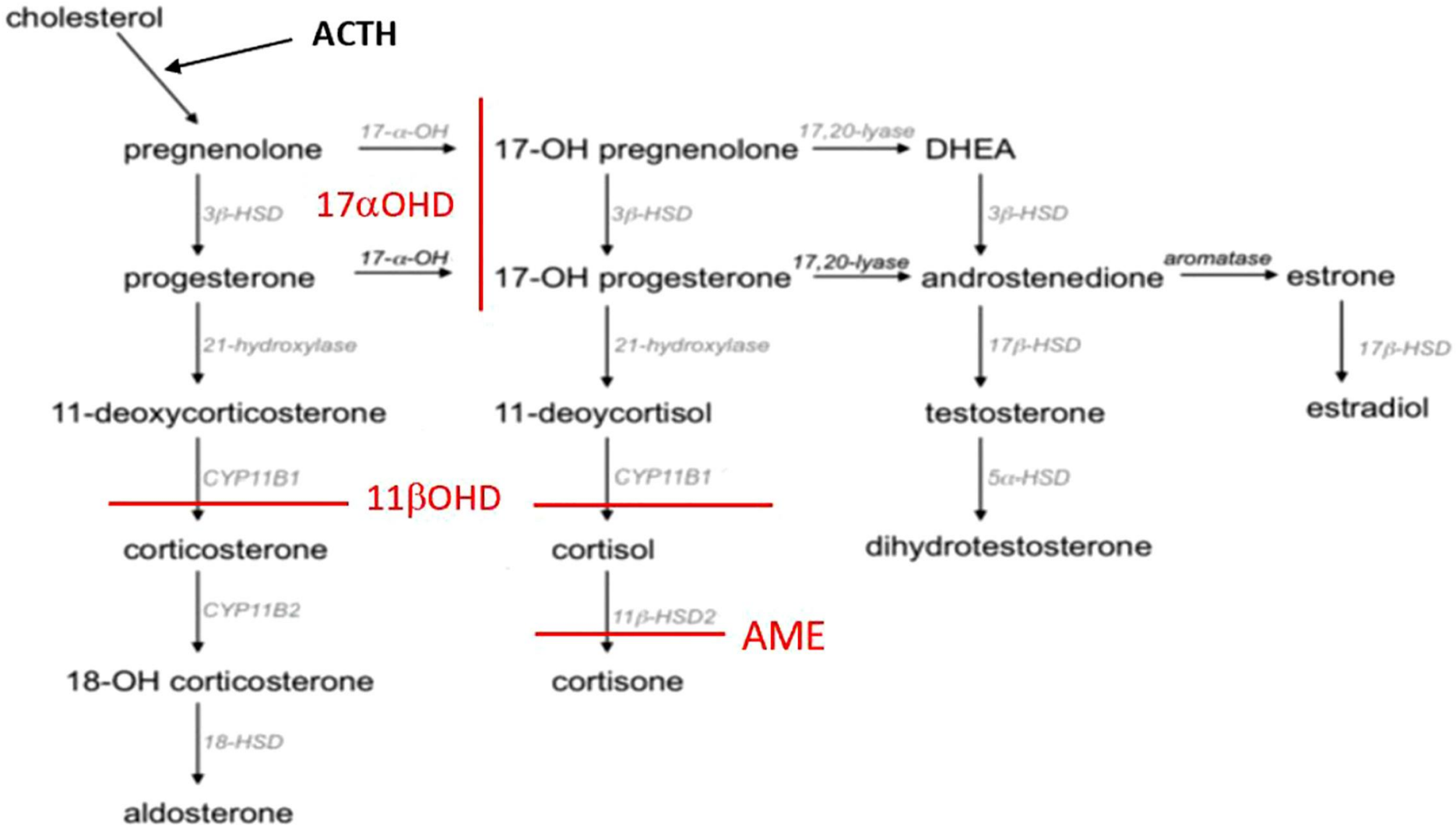
Διευθυντής Γενετικής του Ανθρώπου & Ιατρικής Ακριβείας,
ΙΜΒΒ, ΙΤΕ, Ηράκλειο, Κρήτης


Initial Testing
Secondary Testing
Urinalysis
Blood electrolytes and creatinine
Complete blood count
Any Abnormality
1. Possible Glomerulopathy
▪ Serum C3 and C4
▪ Consider ANA, anti-ds DNA, ANCA
2. Possible bilateral PKD or CAKUT
• Renal ultrasound
All Normal
Normal
Severe Hypertension
1. Non-Invasive renal angiography
2. Echocardiogram
Renal Ultrasound
Negative Angiogram
LVH
Severe Sustained Hypertension
Normal
Mild Hypertension
1. Renal nuclear Scan
2. Plasma Renin, Aldosterone, Cortisol
3. Consider Genetic Analysis
Likely primary hypertension
If older child who fits typical
clinical pattern (see text)


Suspected Monogenic Hypertension
-Negative initial workup
-Electrolyte abnormalities (↑ or ↓K+, ↑ or ↓ H+)
-Significant family history
Low Renin level
Low Aldosterone
Normal /Elevated aldosterone or
Aldosterone to plasma renin activity ratio >30
.iddle syndrome (SCNN1A, SCNN1B, SCNN1G)
Apparent mineralocorticoid Excess (HSD11B2)
Geller syndrome (NR3C2)
11 β-Hydroxylase Deficiency (CYP11B1)
17 α-Hydroxylase Deficiency (CYP17A1)
Gordon Syndrome (WNK1, WNK4, KLHL3 and CU
Primary hyperaldosteronism (adrenal adenoma, a
hyperplasia)
Familial Hyperaldosteronism-I/ GRA (CYP11B1/C
gene)
Familial Hyperaldosteronism-II (CLCN2)
Familial Hyperaldosteronism-III (KCNJ5)
Familial Hyperaldosteronism-IV (CACNA1H)


A
Kidney cortex
Renal vein
Renal artery
Renal pelvis
Ureter
isolated nephron:
DCT
Na+
H+
Na+
Cl−
NCC
Na+
K+
K+
B
KLHL3
CUL3
Gordon Syndrome
WNK1
WNK4
DCT
Na+
H+
Na+
Cl−
NCC
K+
ROMK
Na+
K+
K+
C
CD
Na+
ENaC
ROMK
K+
Maxi-K
Na+
K+
K+
D
Liddle syndrome
CD
Na+
ENaC
ROMK
K+
Maxi-K
Na+
K+
K+


CCD
Na+
ENaC
Na+
K+
ROMK
K+
K+
MR
Maxi-K
11HSD2
Aldosterone
Cortisone
Cortisol

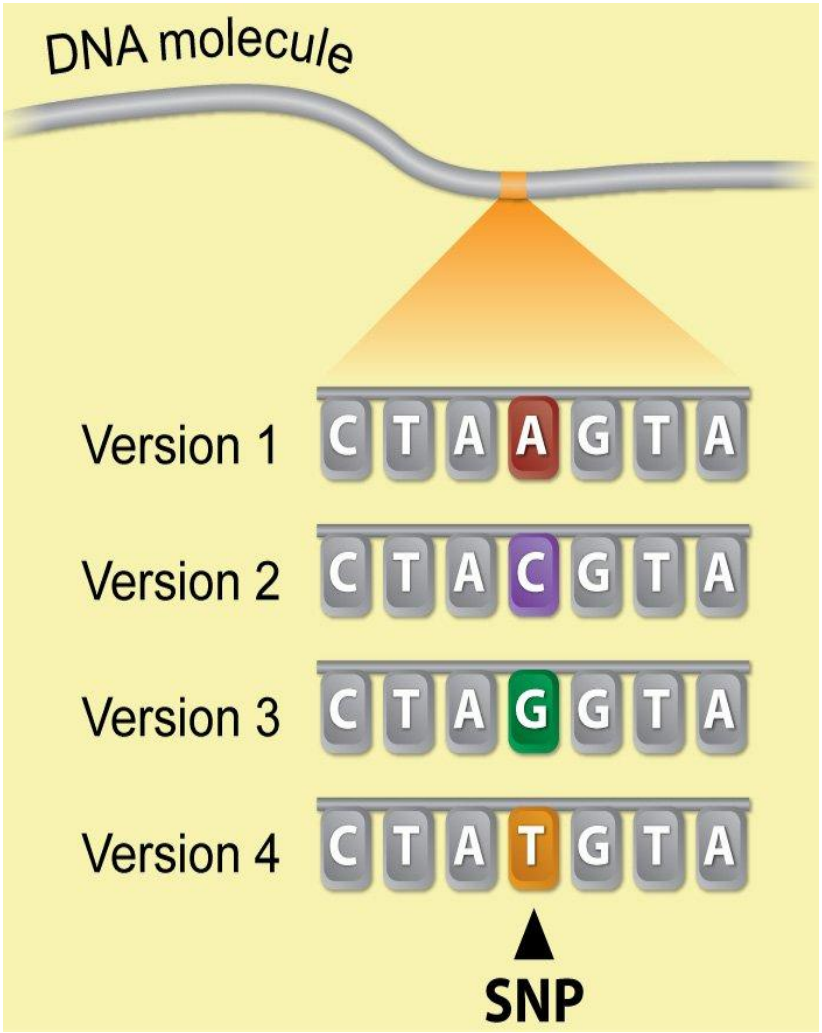


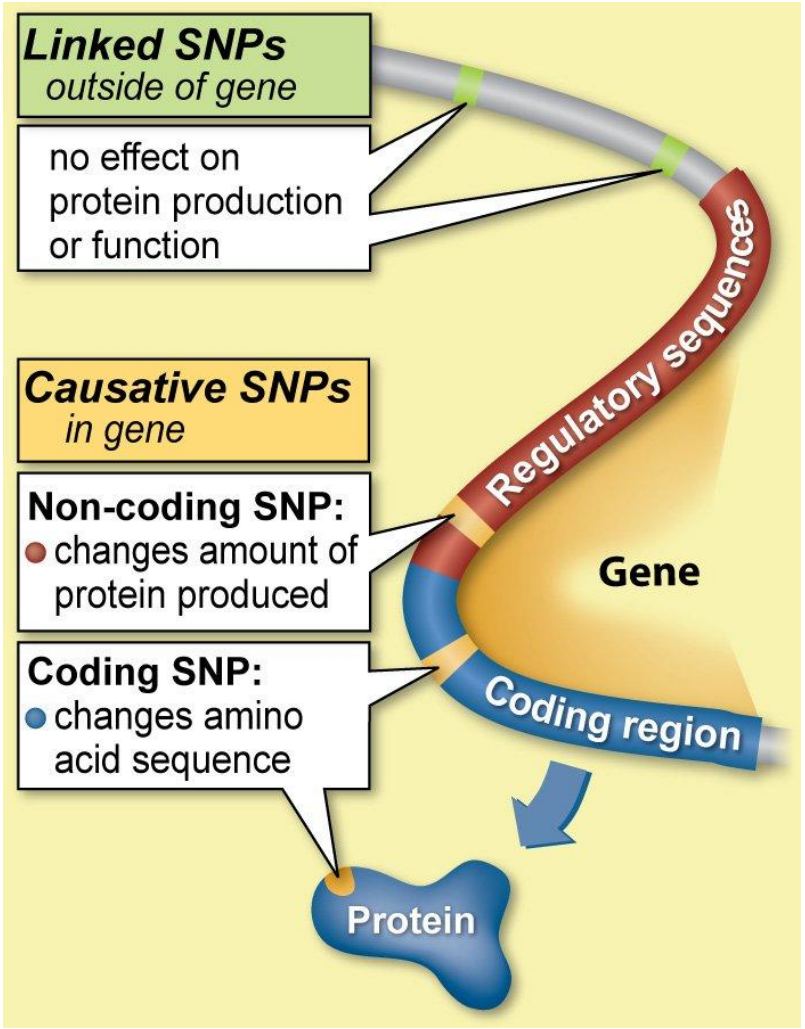
Zona Glomerulosa
Mineralocorticoid synthesis

Zona Fasciculata
Glucocorticoid synthesis

Zona Reticulata
Androgen/Estrogen synthesis

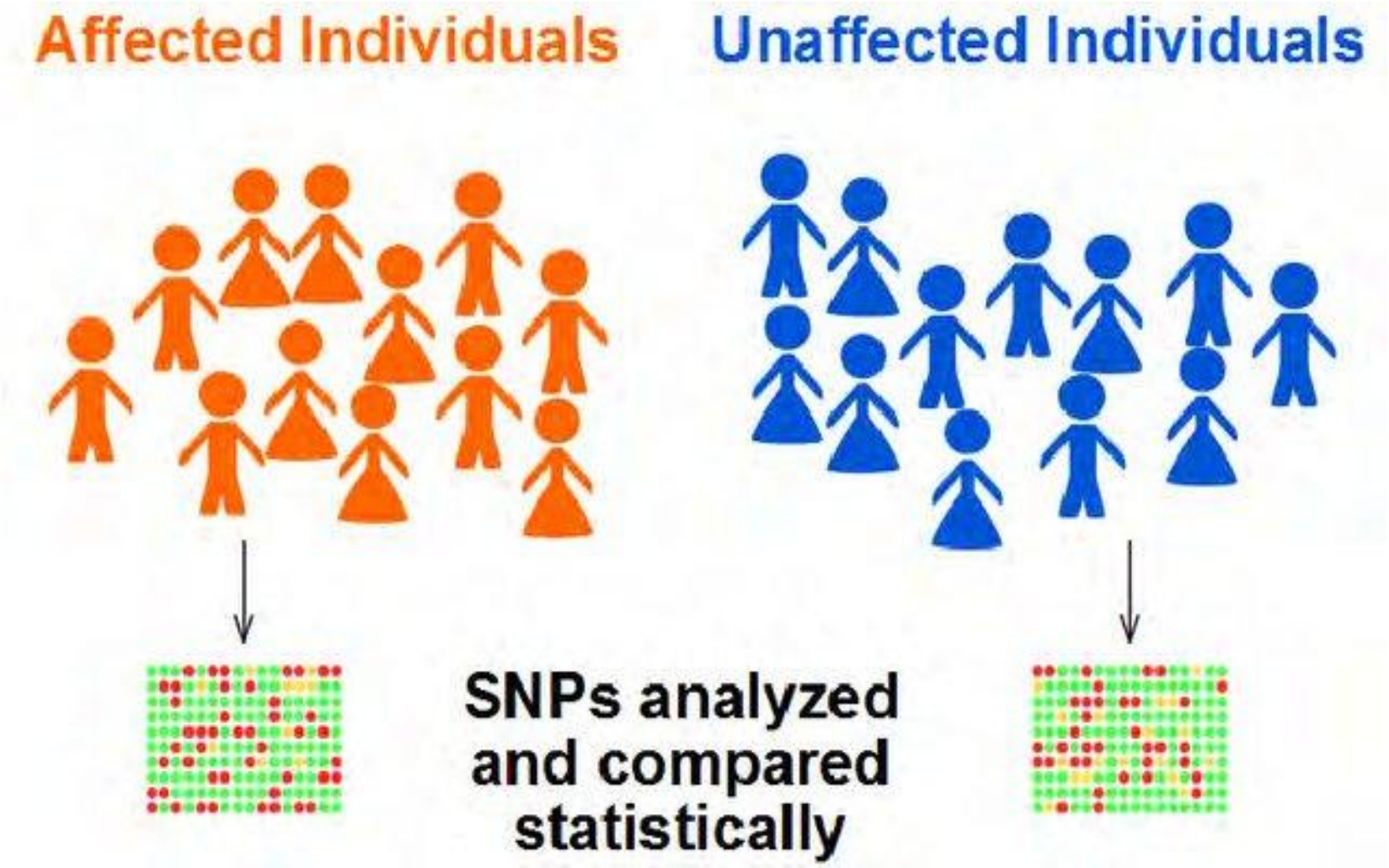
Comprehensive map of the genome: single nucleotide polymorphisms (SNPs)



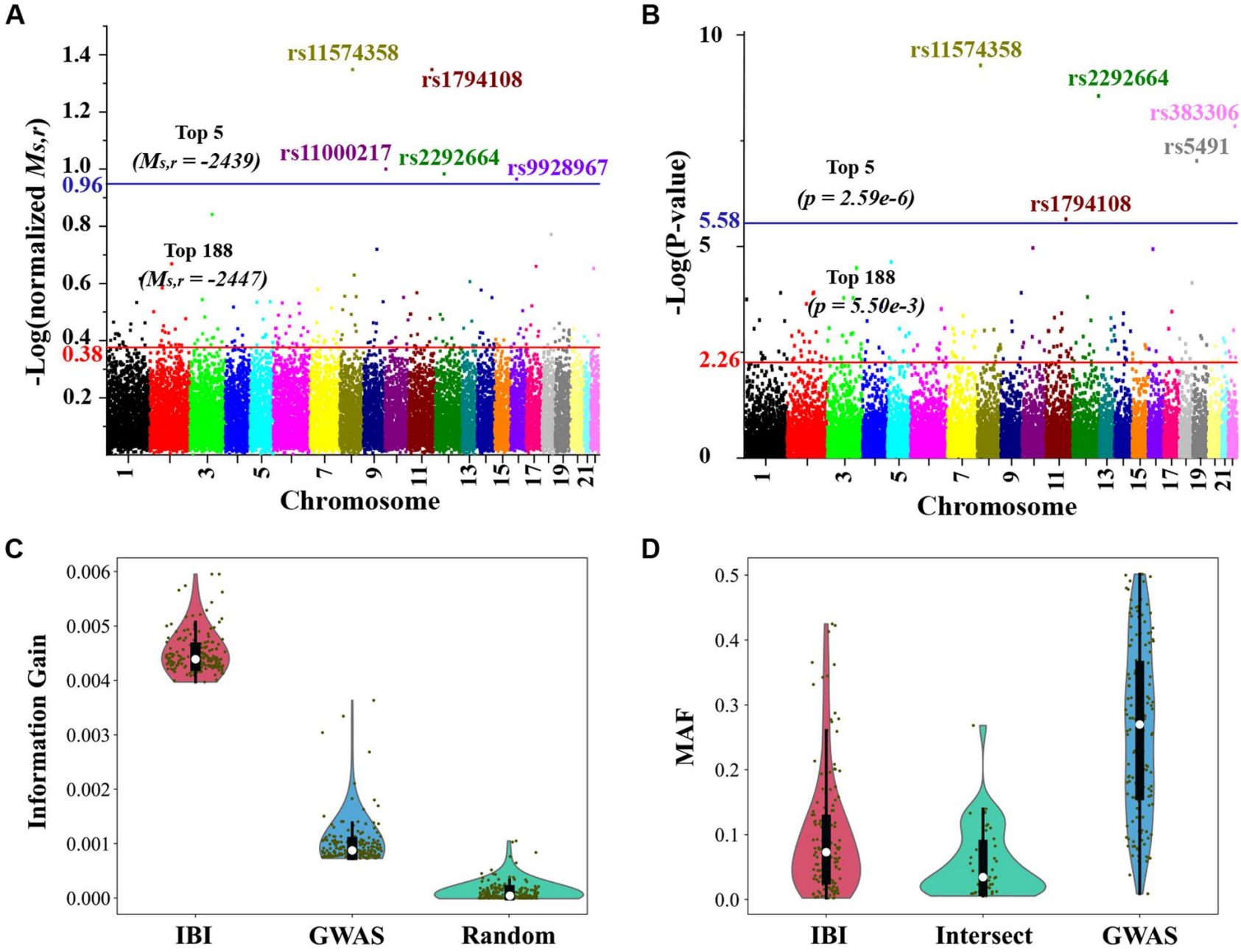


https://learn.genetics.utah.edu/content/precision/snips

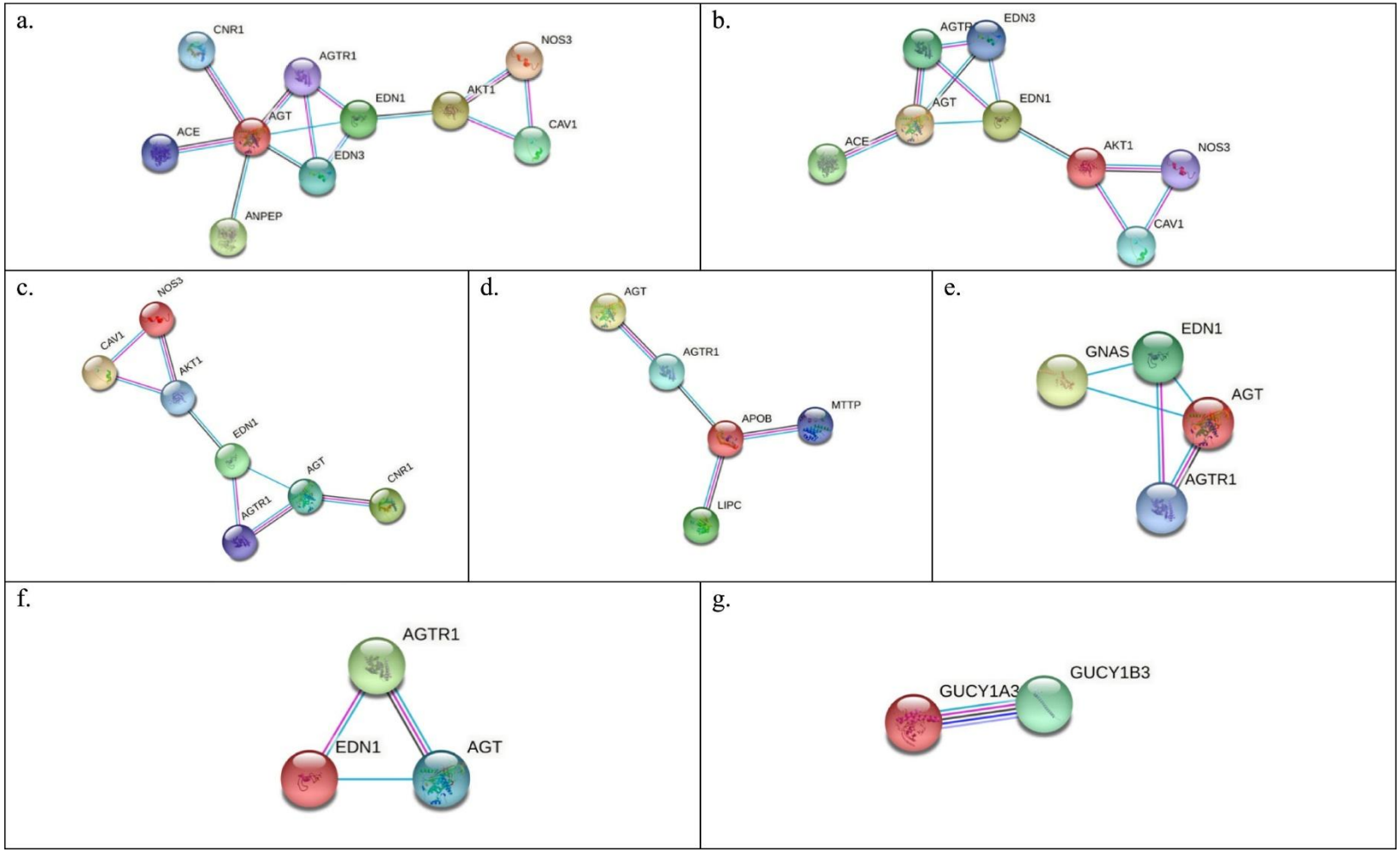
Genome-wide association studies (GWAS)



https://www.researchgate.net/publication/221929527



BMC Genomics 2023 Nov 7;23(Suppl 5):863. doi: 10.1186/s12864-023-09757-9



GENE 2023 Nov 8:894:147973.

doi: 10.1016/j.gene.2023.14797

ENDOCRINE CAUSES OF HYPERTENSION

- Endocrine HTN
  - **Adrenal Hypertension**
  - Hyperparathyroidism
  - Hyperthyroidism
  - Acromegaly; growth hormone excess

ADRENAL HYPERTENSION

Low Renin HTN

Adrenal Medulla

- Pheochromocytoma

Adrenal Cortex

- Cushing's Syndrome
- Primary Hyperaldosteronism
- Congenital Adrenal Hyperplasia (11β or 17α deficiency)
- Familial Glucocorticoid Resistance
- Apparent Mineralocorticoid Excess

Cushing's Syndrome

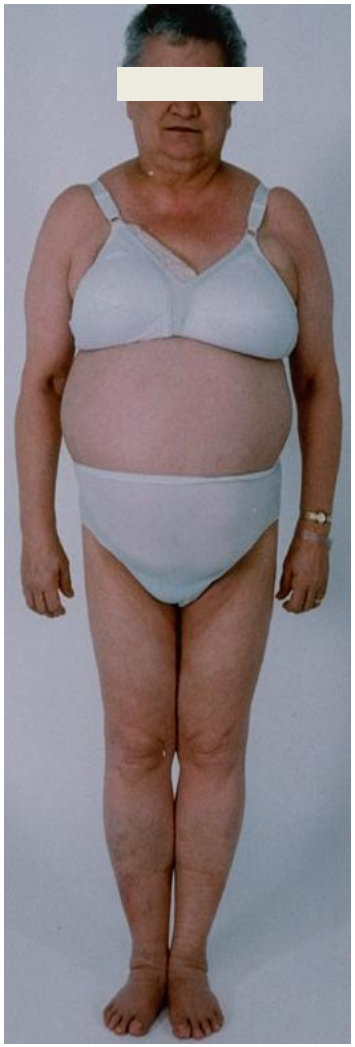
- A symptom complex that reflects excessive tissue exposure to cortisol

- The diagnosis cannot be made without both clinical and biochemical signs of hypercortisolism

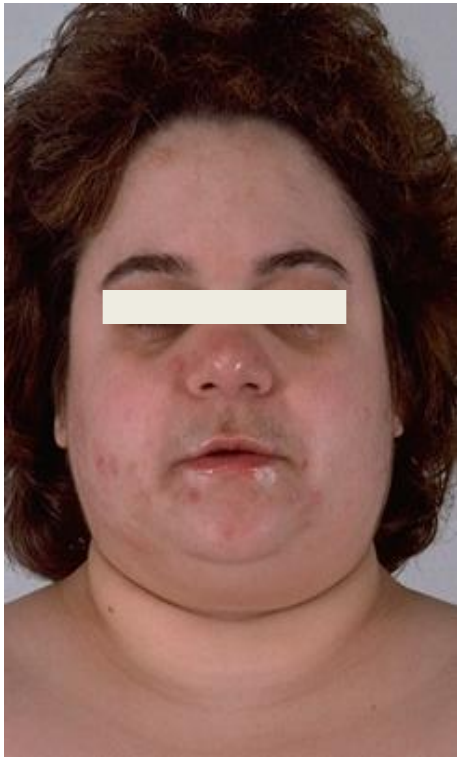
Signs and Symptoms of Cushing's

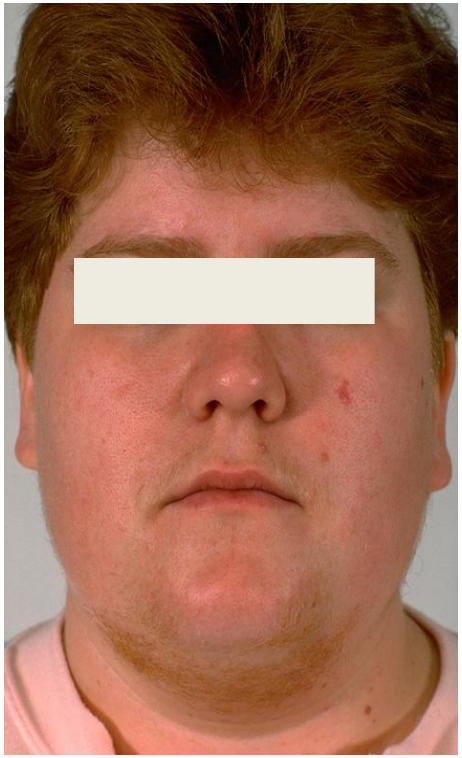
SIGN/SYMPTOM	%	SIGN/SYMPTOM	%
Decreased libido	100	EKG abn/atherosclerosis	55
Obesity/weight gain	97	Dorsal fat pad	54
Plethora	94	Edema	50
Round face	88	Abn glucose tolerance	50
Menstrual changes	84	Osteopenia or fracture	50
Hirsutism	81	Headache	47
Hypertension	74	Backache	43
Eccymoses	62	Recurrent infections	25
Lethargy, depression	62	Abdominal pain	21
Striae	56	Acne	21
Weakness	56	Female balding	13

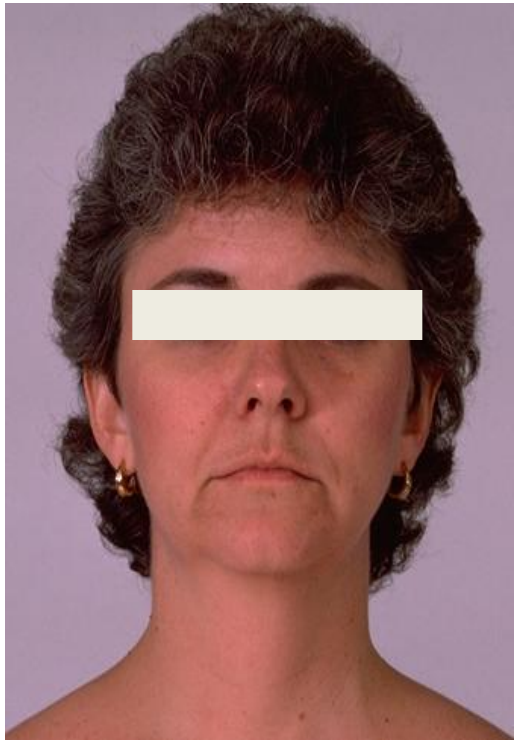
Body Habitus



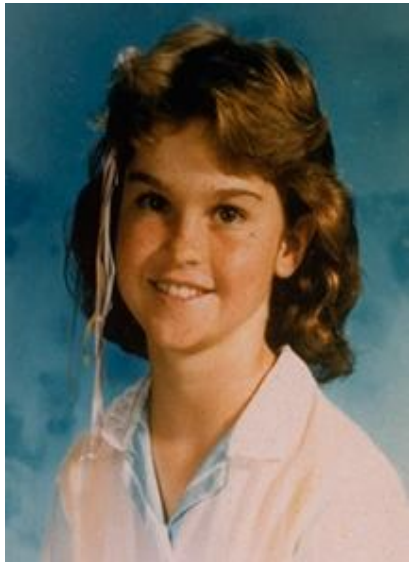
Facial Fullness







Photographs




Continuum Of Clinical Certainty

Dorsocervical hump
Simple obesity

Gonadal
Psychiatric
Cognitive
Weight

Skin
Hypertension

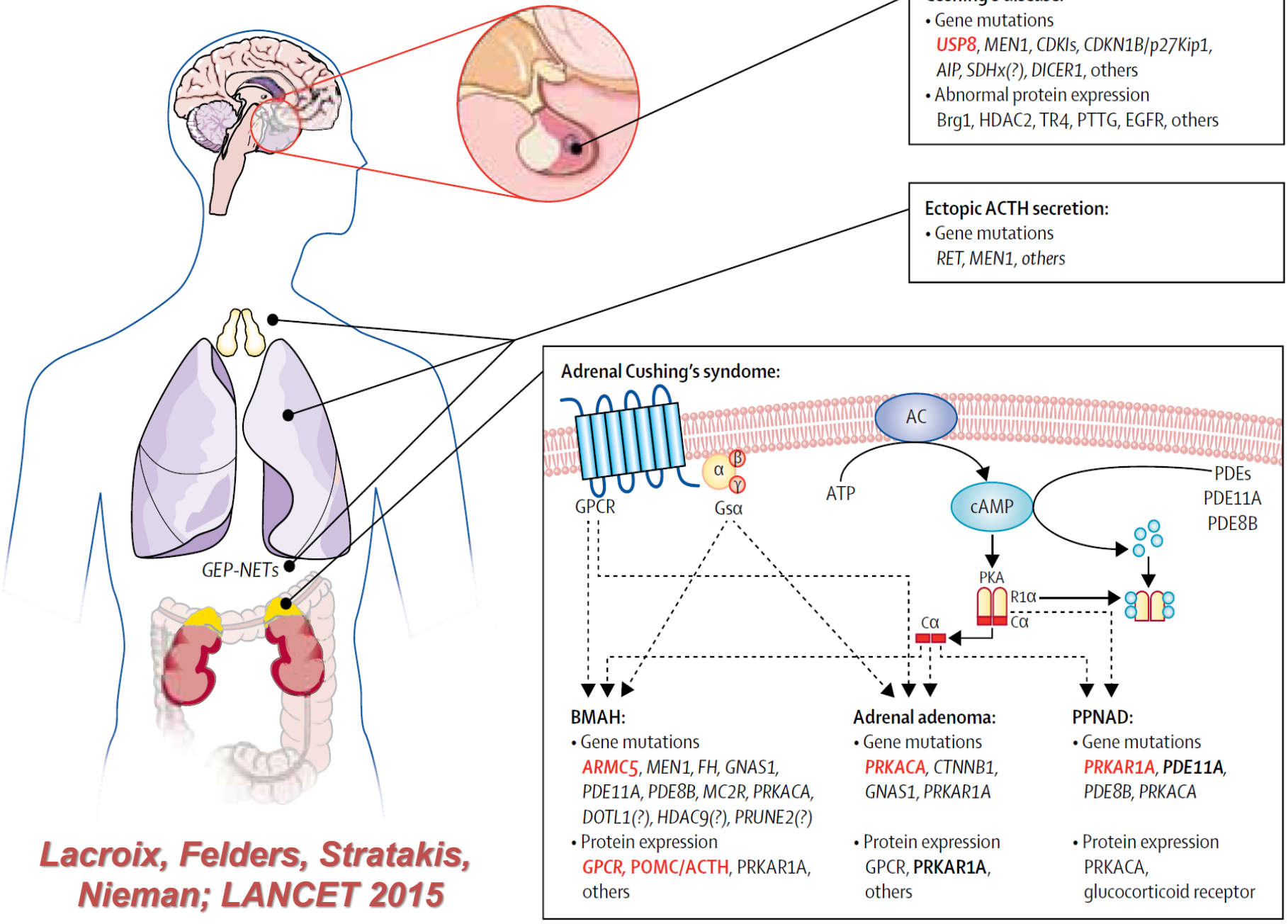
Purple striae
Osteopenia
Weakness

Biochemical Tests For Cushing's Syndrome

- Guidelines from the Endocrine Society (J Clin Endocrinol Metab June 2008)
- UFC greater than upper normal range
- 1 mg Dexamethasone suppression test
  - Cortisol >1.8 ug/dL
- Bedtime salivary cortisol - cutpoints differ (> 4 nmol/L)

Causes of Cushing's Syndrome

Exogenous	Endogenous
Most common cause of CS **Factitious or iatrogenic** **Glucocorticoid or ACTH**	**ACTH-independent (20%)** **• adenoma or carcinoma** **• rarely, bilateral hyperplasia**
	ACTH-dependent (80%) **• corticotroph adenoma (85%)** **• ectopic ACTH secretion (15%)** **• rarely, ectopic CRH**



Lacroix, Felders, Stratakis, Nieman; LANCET 2015

Primary Hyperaldosteronism (PA)

- Aldosterone production *inappropriately high*
- Aldosterone production *relatively autonomous*
- Aldosterone production *non-suppressible by sodium loading*

Primary Hyperaldosteronism Disorders

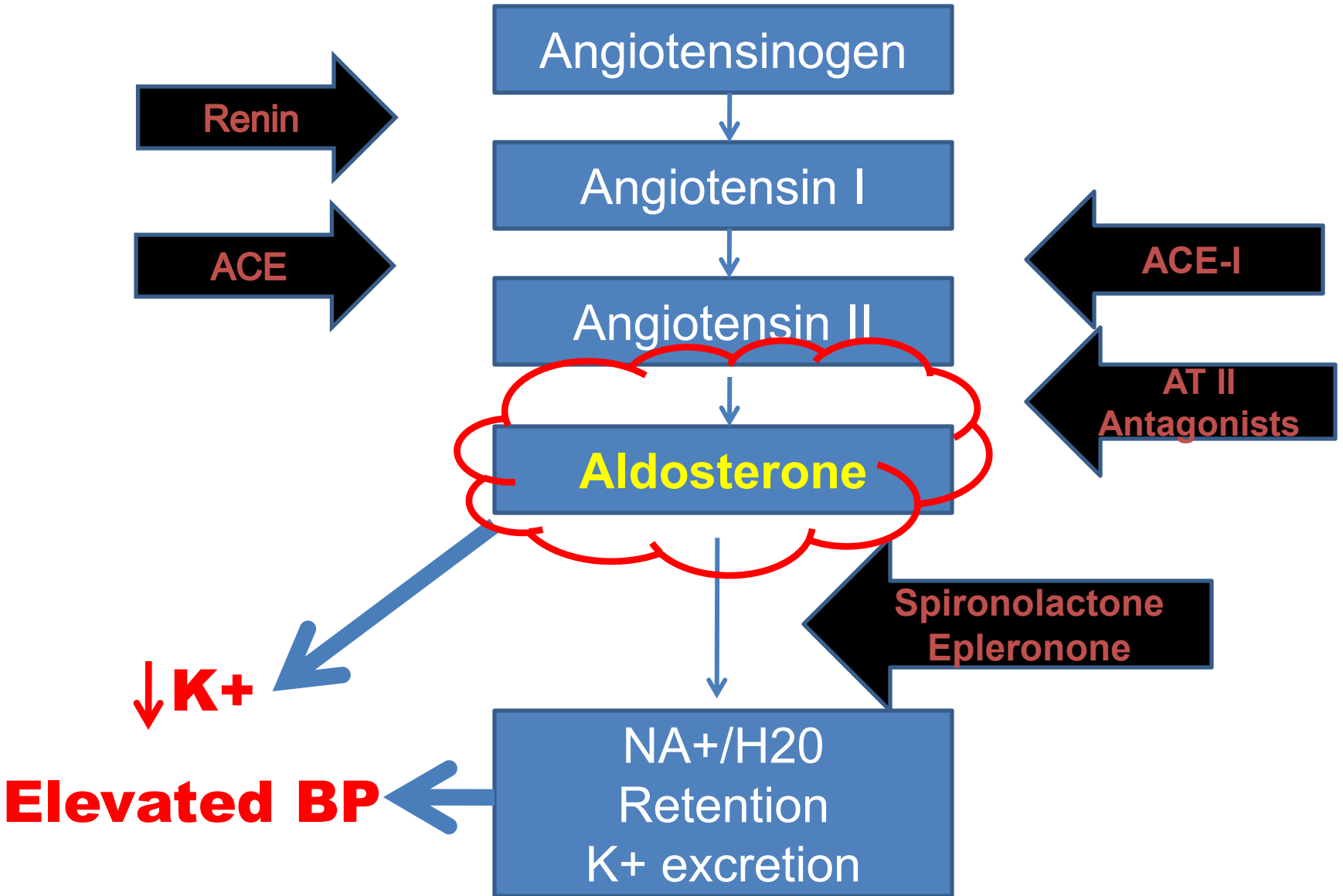
- Unilateral Disease
  - Adenoma (APA) vs. Hyperplasia (PAH)
- Bilateral Disease
  - Adenoma (rare) vs. Hyperplasia (IHA)
- Aldosterone Producing Adrenocortical Carcinoma
- Genetic Diseases
  - Familial Hyperaldosteronism type I (Glucocorticoid Remediable Aldosteronism)
  - Familial Hyperaldosteronism type II)

Groups with high prevalence of primary hyperaldosteronism

Moderate/severe hypertension (stages based on JNC 7)	Overall: 6.1% Stage 1 (mild): 2% Stage 2 (moderate): 8% Stage 3 (severe): 13%
Resistant Hypertension (defined as BP of < 140/90 despite treatment with 3 anti-hypertensive meds	17-23%
Hypertensive patients with spontaneous or diuretic induced hypokalemia	NA
Hypertension with adrenal incidentaloma	Median 2% (range, 1.1%-10%)

Case Detection, Diagnosis, and Treatment of Patients
With Primary Aldosteronism: An Endocrine Society Clinical Practice Guideline

The Renin-Angiotensin-Aldosterone System



Diagnosis of Hyperaldosteronism: Clinical Presentation

- Hypertension is common ranging form mild and intermittent to persistent and severe.
  - Normotensive primary aldosteronism has been described but is exceedingly rare.
- Hypokalemia
  - frequent cramps, fatigue, muscle weakness, nocturia
- A
- Hypocalcemia (rare): paresthesias, prolonged QT interval

-Absence of hypokalemia does NOT exclude the diagnosis
-**Normokalemic hypertension** is the most common clinical presentation

Screening

Aldosterone to Renin Ratio (ARR)

-PAC/PRA -

> 30 likely diagnosis of PA

< 20 unlikely diagnosis of PA

Pitfalls in Diagnosis

- Renin assays
  - Lack of assay precision at low levels
  - Lower limit, e.g. <0.6 vs 0.2
- Variability in measurements
  - Time of day, food intake, posture, tumor production variability
- Medication interference
- Potassium level
  - Hypokalemia suppresses aldosterone secretion

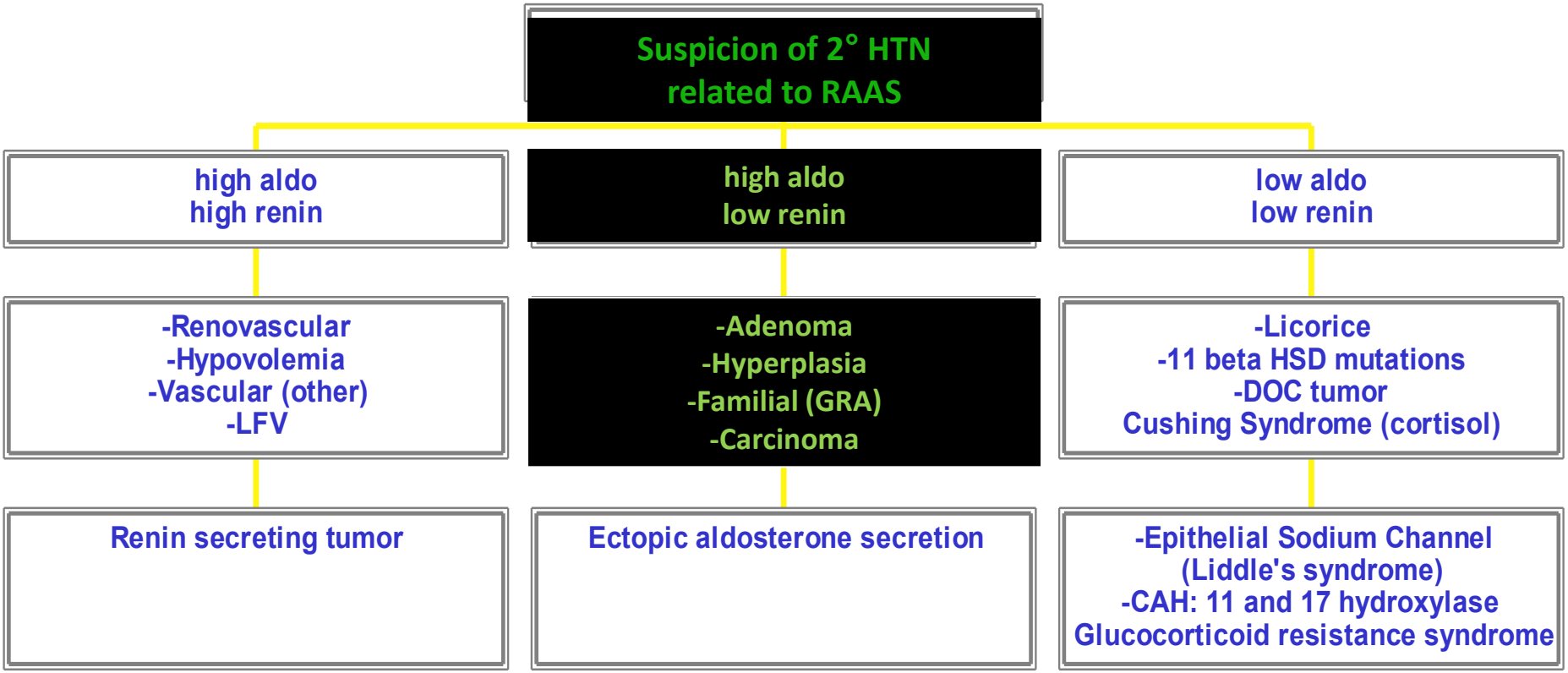
  REPEAT THE SCREENING TEST (ARR)

Anti-hypertensives used during screening and confirmation of PA

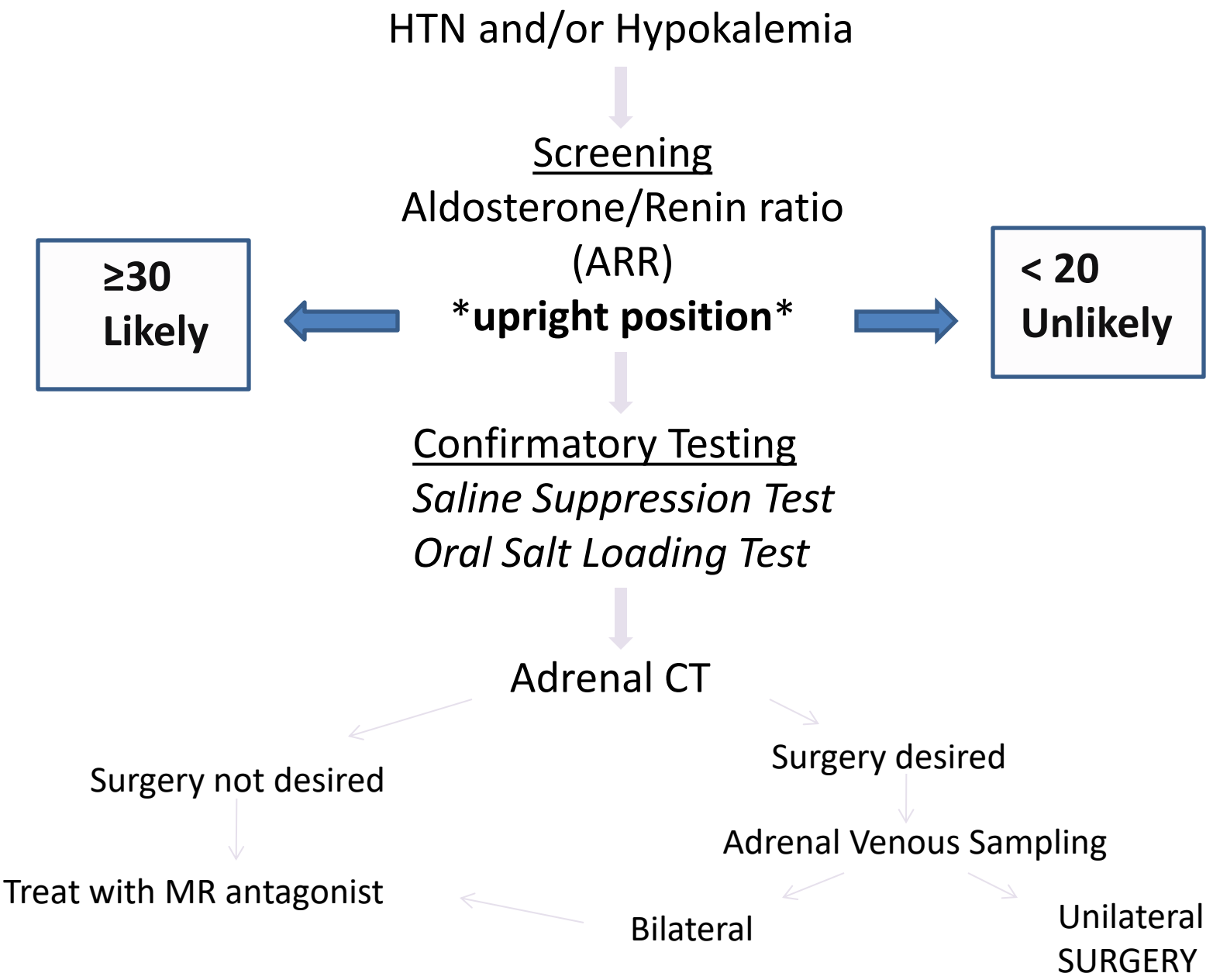
Verapamil slow-release non-dihydropyridine calcium channel antagonist	90-120-mg twice daily
Prazosin hydrochloride alpha-adrenergic blocker	0.5-1 mg two to three times daily, increasing as required
Doxazosin mesylate alpha-adrenergic blocker	1-2 mg once daily, increasing as required
Terazosin hydrochloride alpha-adrenergic blocker	1-2 mg once daily, increasing as required
Hydralazine vasodilator	12.5 mg twice daily, increasing as required

Hyperaldosteronism:

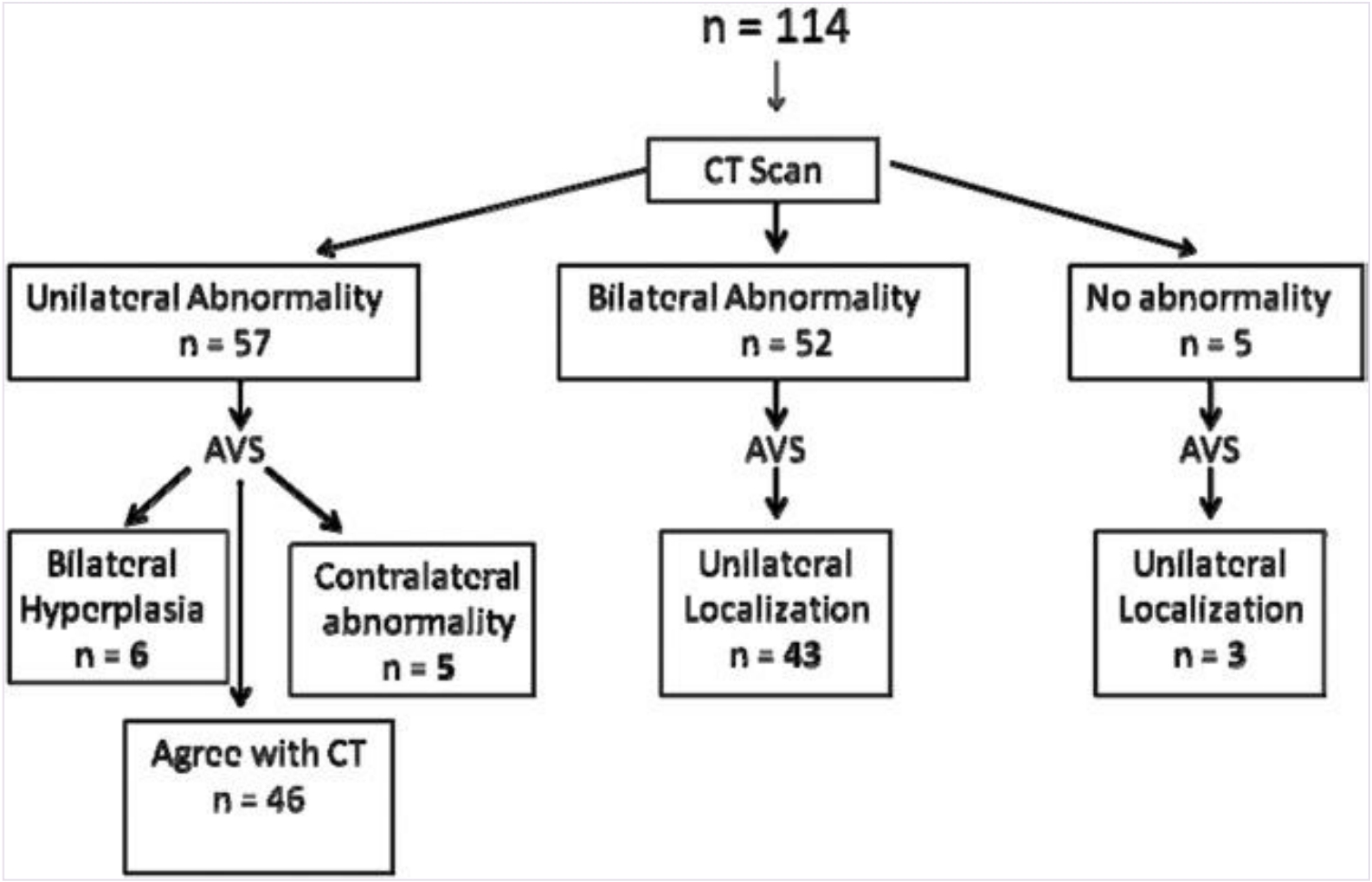
Differential Diagnosis of HTN and Hypokalemia



Primary Aldosteronism Dx Algorithm



Necessity of Adrenal Venous Sampling (AVS)



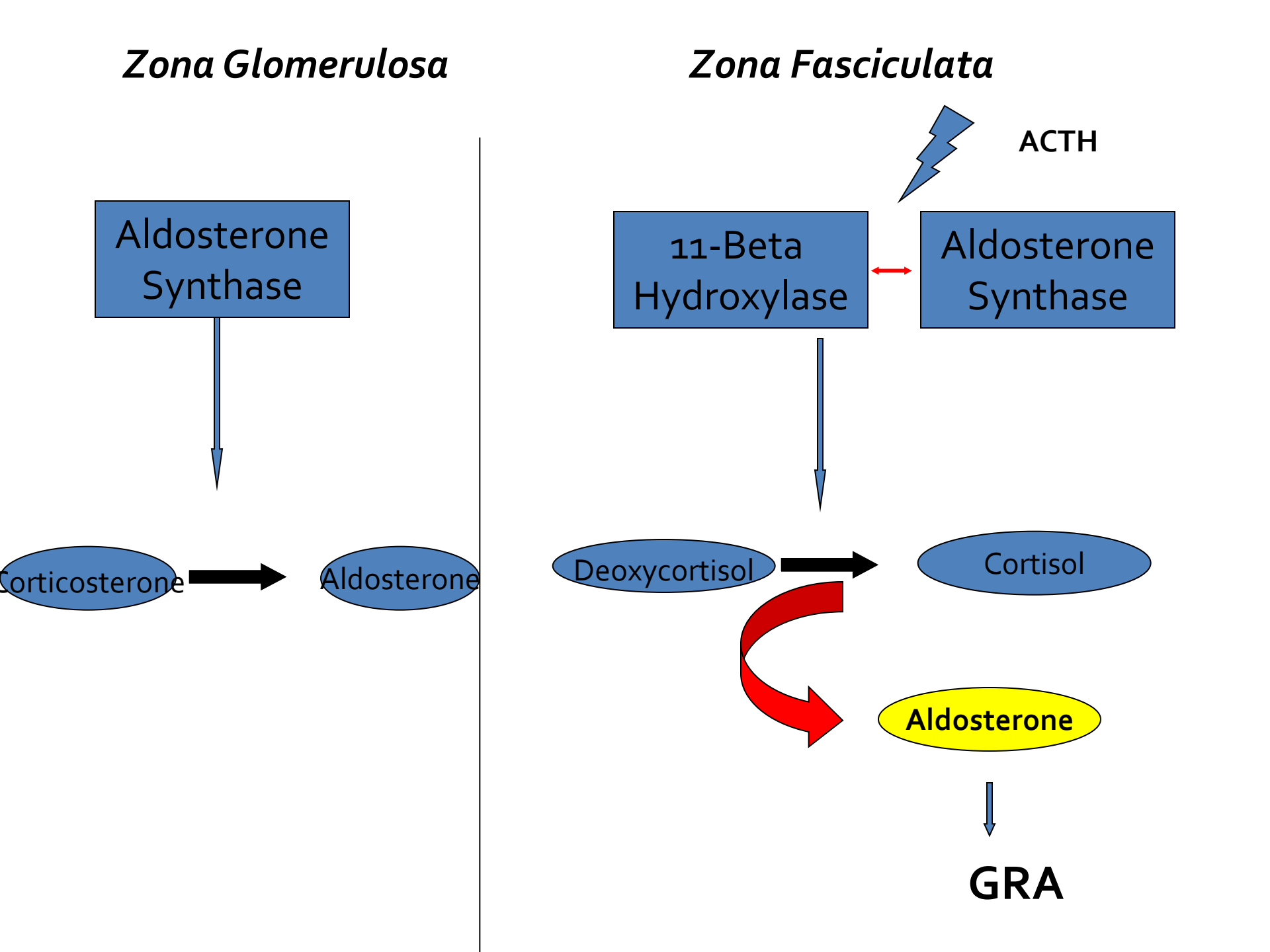
Mathur A et al. J Am Coll Surg 2010
Nwariaku FE et al. Arch Surg 2006

Familial Forms of PA

- Familial Type I : Glucocorticoid Remediable Aldosteronism (GRA)
- Familial Type II : APA or BAH
- Familial Type III-V : Recently described

Glucocorticoid Remediable Aldosteronism (FH type I)

- Autosomal Dominant
- Defect: Cross-over of genetic material between highly homologous genes that code for the enzyme 11β-hydroxylase (CYP11B1 – catalyzes last step in cortisol synthesis) AND the gene for aldosterone synthesis (CYP11B2)
- ACTH-responsive promoter fused with the coding region of CYP11B2 allows *aldosterone synthesis to be strongly regulated by ACTH*


Zona Glomerulosa
Zona Fasciculata
ACTH
Aldosterone Synthase
11-Beta Hydroxylase
Aldosterone Synthase
Corticosterone
Aldosterone
Deoxycortisol
Cortisol
Aldosterone
GRA

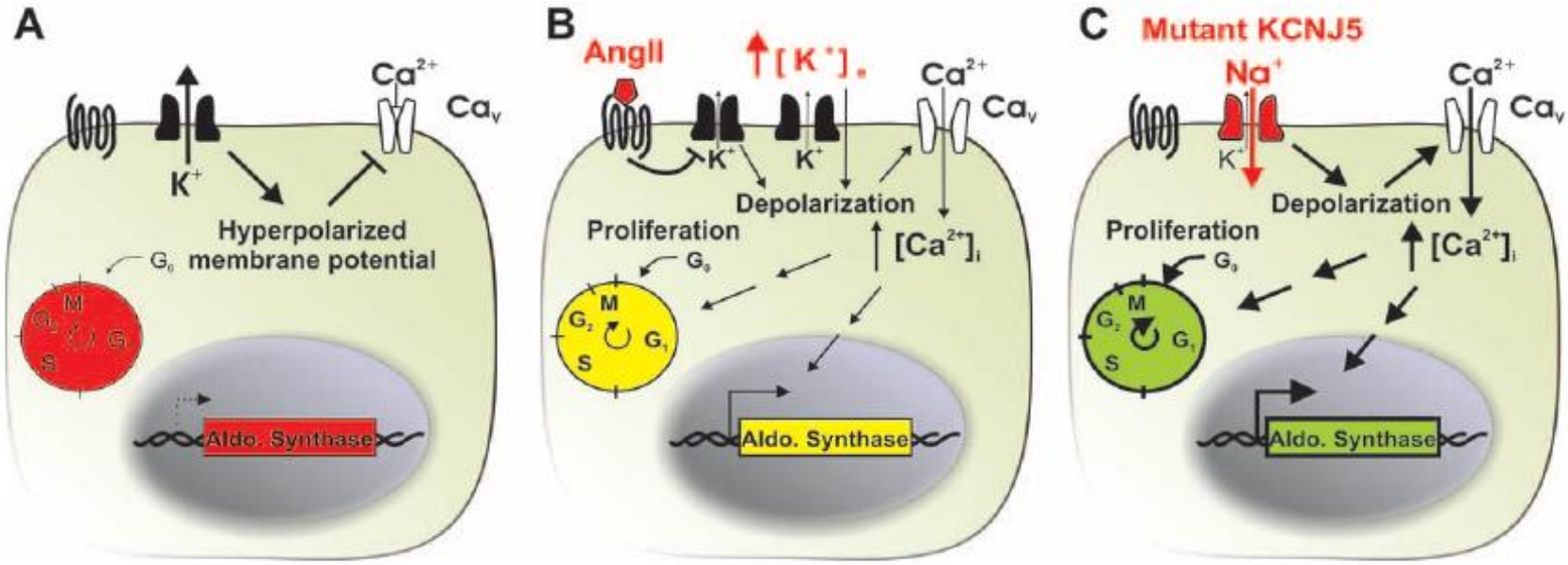
A novel genetic locus for low renin hypertension: familial hyperaldosteronism type II maps to chromosome 7 (7p22)

J Med Genet 2000;37:831–835

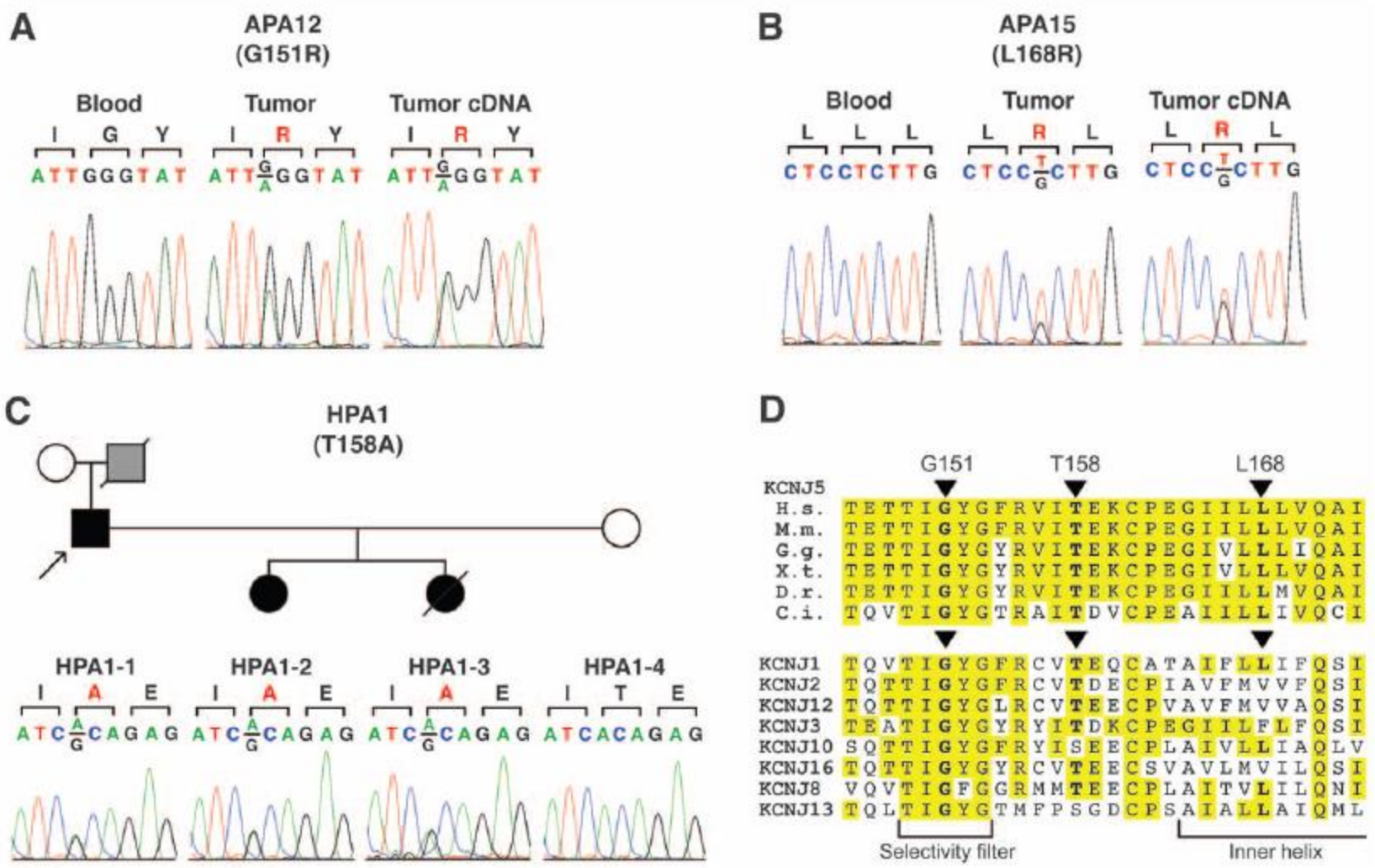
K^+ Channel Mutations in Adrenal Aldosterone-Producing Adenomas and Hereditary Hypertension

11 FEBRUARY 2011 VOL 331 **SCIENCE**

Murim Choi,[1] Ute I. Scholl,[1] Peng Yue,[2*] Peyman Björklund,[3,4*] Bixiao Zhao,[1*] Carol Nelson-Williams,[1] Weizhen Ji,[1] Yoonsang Cho,[5] Aniruddh Patel,[1] Clara J. Men,[1] Elias Lolis,[5] Max V. Wisgerhof,[6] David S. Geller,[7] Shrikant Mane,[8] Per Hellman,[4] Gunnar Westin,[4] Göran Åkerström,[4] Wenhui Wang,[2] Tobias Carling,[3] Richard P. Lifton[1]†

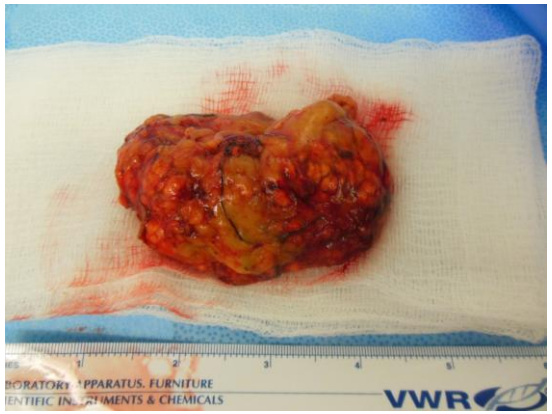


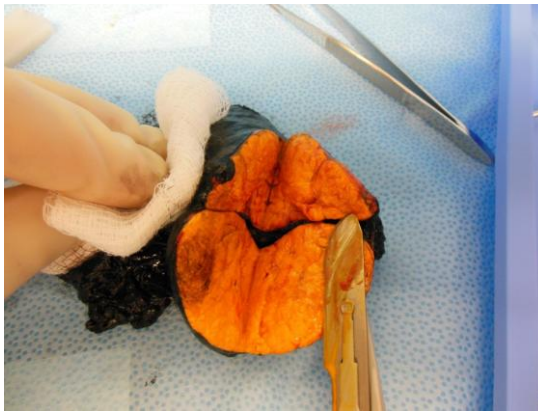
NATIONAL INSTITUTES OF HEALTH

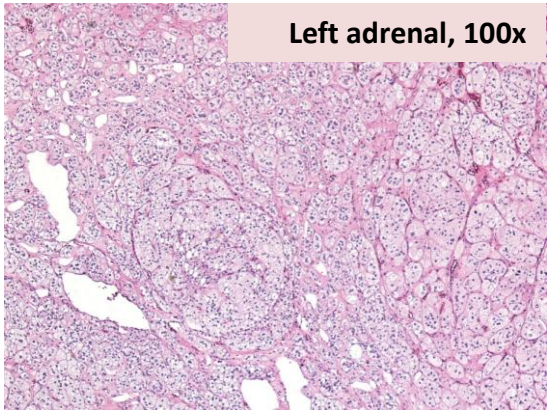


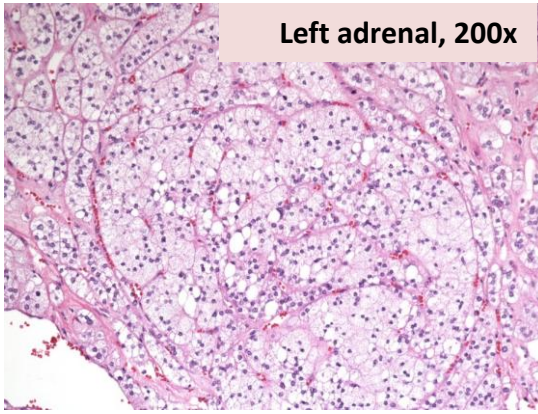
CLINICAL PRESENTATION OF AN NIH PATIENT

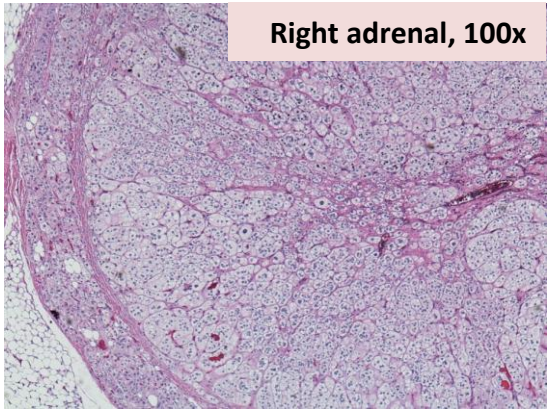
- 19 years old F with de novo germ line *KCNJ5* mutation (p.Glu145Gln) leading to bilateral adrenal hyperplasia
- Complications of hyperaldosteronism
  - chronic kidney disease
  - proteinuria 1.9 g/24h
  - aortic root dilatation
- Post-operatively - standard dose of fludrocortisone not sufficient to control rising potassium

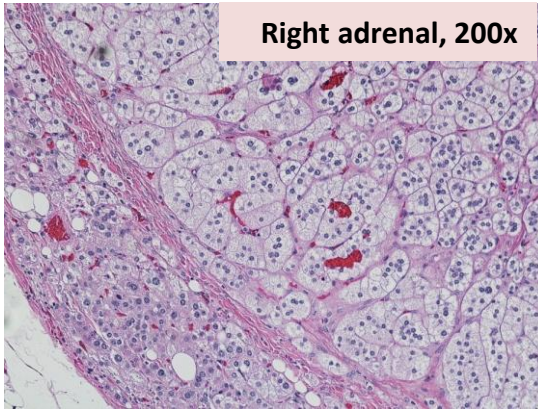






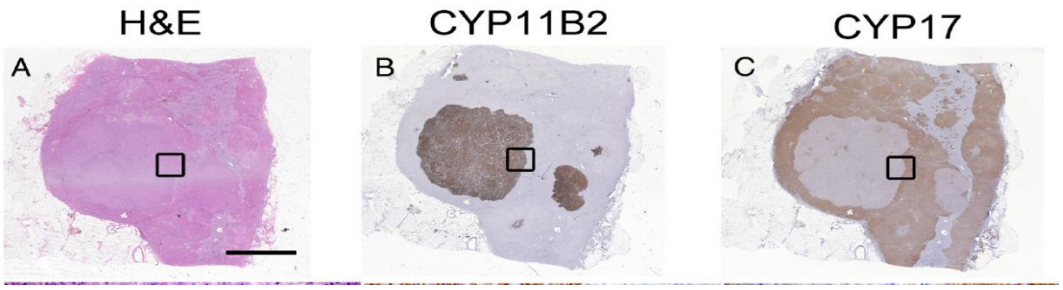






Molecular Heterogeneity in Aldosterone-Producing Adenomas

Kazutaka Nanba, Andrew X. Chen, Kei Omata, Michelle Vinco, Thomas J. Giordano, Tobias Else, Gary D. Hammer, Scott A. Tomlins, and William E. Rainey



J. Clin. Endocrinol. Metabol. 2016; 101(3): 999-1007

Table 1. Somatic Mutations Identified in CYP11B2-Positive Tumor Regions

Case	Sample	Gene	Reference Allele	Variant Allele	Amino Acid Change	FAO	FDP	Variant Allele Frequency (FAO/FDP), %	Variant Allele Frequency in Matched CYP11B2-Negative Tumor Region/Nodule
1	B2T1	*CACNA1D*	T	G	F747C	151	566	27	0
2	B2T1	*KCNJ5*	T	G	L168R[a]	110	463	24	0
3	B2T1	*ATP1A1*	T	G	L104R[a]	569	1664	34	0
4	B2T1	*CTNNB1*	C	T	S45F[b]	190	536	35	39
6	B2T1	*ATP2B3*	GTGCTG		L424_V425del[a]	292	445	66	N.A.
	B2T2	*KCNJ5*	G	A	G151R[a]	149	1998	7	N.A.
	B2T2	*ATP2B3*	GTGCTG		L424_V425del[a,c]	47	493	10	N.A.
7	B2T1	*CACNA1D*	T	G	F747V[a]	361	1184	30	0
	B2T2	*ATP1A1*	T	G	L104R[a]	131	786	17	0

PHEO: Important Facts

- Not diagnosed in at least 50% of patients (autopsy series) (“great mimic”)

Key to diagnosis: Think of PHEO

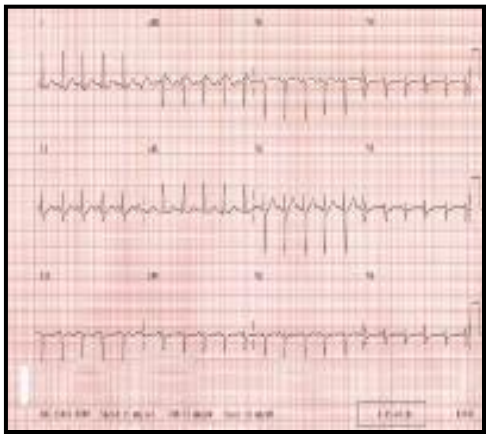
HTN, tachycardia, pallor, sweating, headache, feelings of panic or anxiety are most common

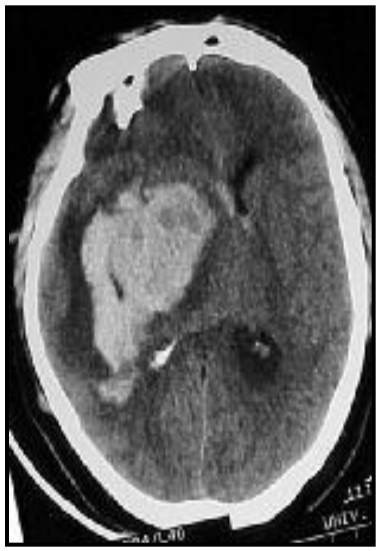
** PAROXYSMS**

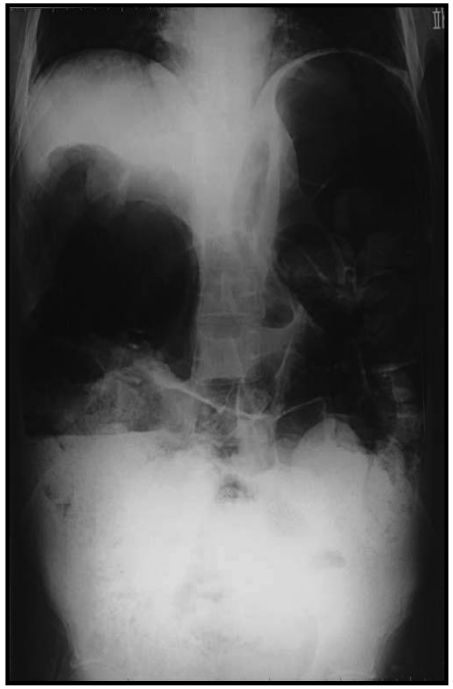
- Malignant: in 15-36% of patients, no reliable markers, no effective treatments

PHEO/PGL as a volcano

The concentrations of catecholamines in PHEO/PGL tissue are enormous (more than 1000 x higher than in plasma), creating a volcano that can erupt at any time (storm, attack, spell).

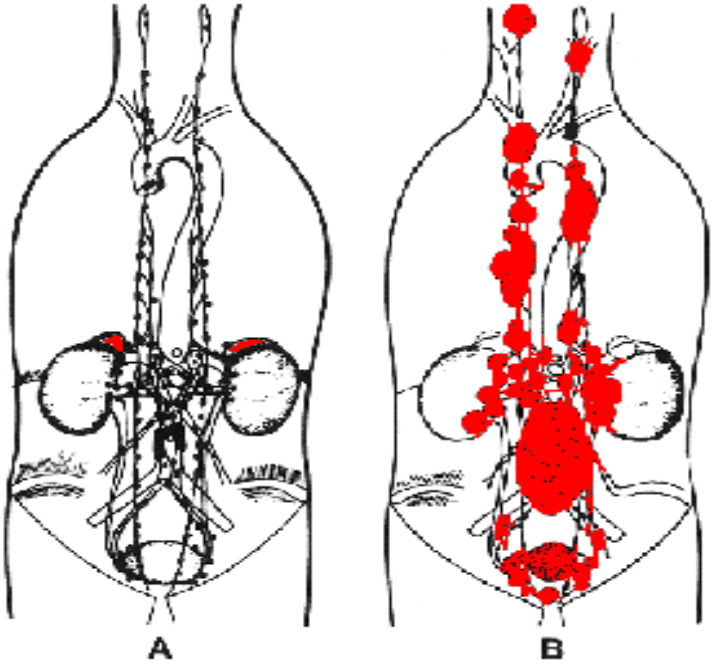






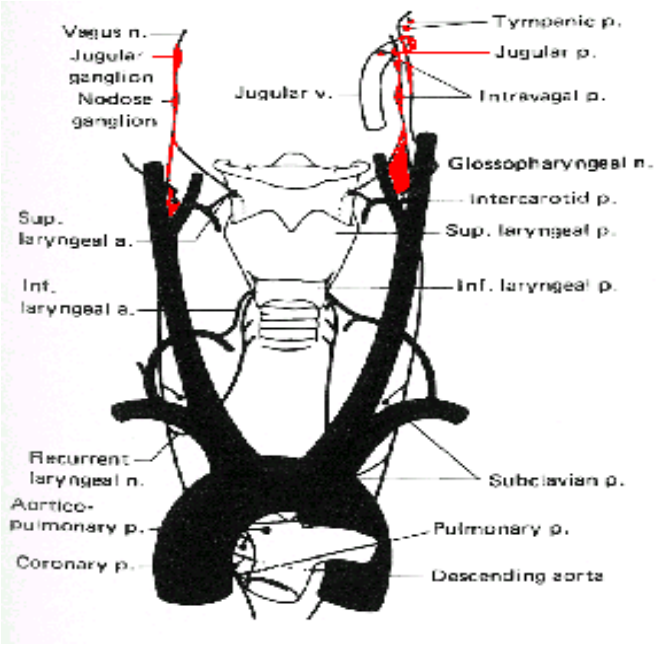
All patients with PHEO/PGL must receive α (β) receptor blockade.

PHEO: Sites of Origin



adrenal PHEO

extra-adrenal PHEO



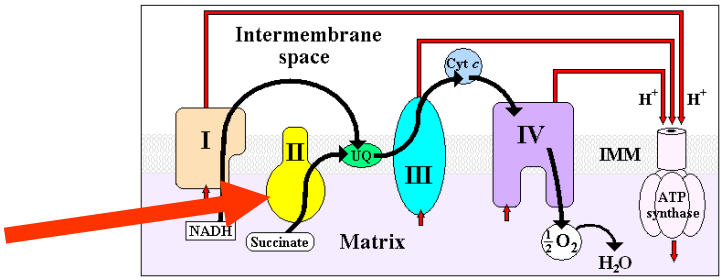
head and neck paraganglioma

PHEO in Syndromes

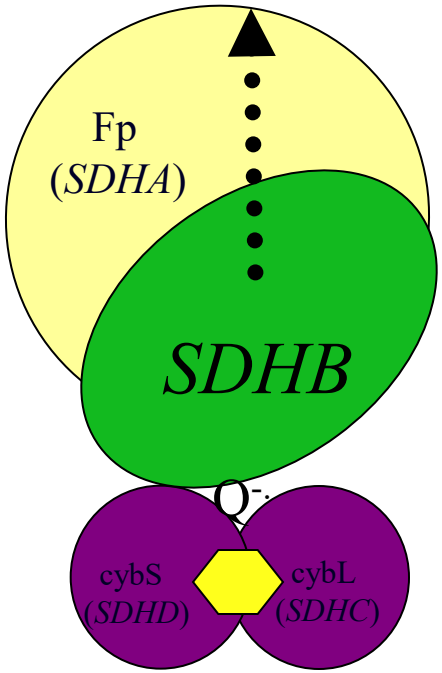
- Von Hippel-Lindau Syndrome
  - Adrenal medulla, norepinephrine producing tumors
  - Up to 25% of patients will develop PHEO
- Multiple Endocrine Neoplasia 2 (MEN 2)
  - 2a – adrenal medulla, epinephrine or epi-and norepinephrine producing tumors, 50% bilateral
- Neurofibromatosis (NF1)
  - 2-5%
  - Epi and norepi secreting tumors

The PGL syndromes: genetics

Succinate dehydrogenase gene family mutations



Succinate → Fumarate



Shift to *glycolysis*: Warburg effect (production of 2 ATP vs 34 ATP by oxphos/Krebs cycle):

↓

Pseudohypoxia or another signaling?

↓

Pseudo-hypoxia promotes GROWTH

↓

PHEO/PGL

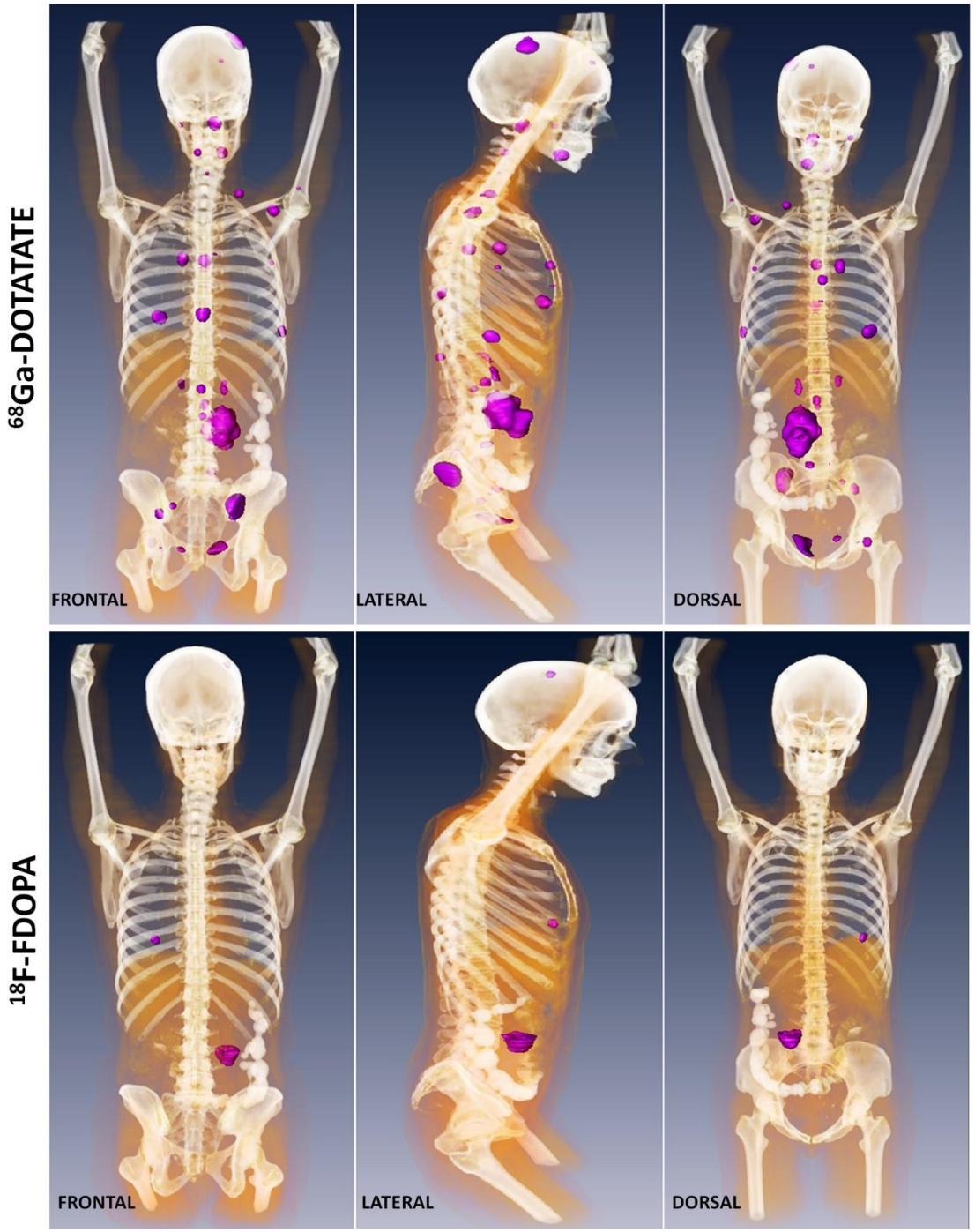
Characteristics of SDHB/D-related PHEOs

SDHB PHEOs

- > 95% extra-adrenal, often secrete NE and DA
- Malignant at initial diagnosis: 30%; follow-up: > 90%
- Family history: 10%
- Younger age of presentation

SDHD PHEOs

- Most of them present as head and neck PGLs
- >90% do not secrete any catecholamines
- >99% benign
- Younger age of presentation


^{68}Ga-DOTATATE
FRONTAL
LATERAL
DORSAL
^{18}F-FDOPA
FRONTAL
LATERAL
DORSAL

SUMMARY - conclusions

- Endocrine hypertension, especially primary hyperaldosetronism is more common than previously thought

- Most of these disorders have a genetic background

- Pheochromocytomas and/or paragangliomas should be actively sought; they are often the result of genetic mutations

Approach to a patient with hypertension and a genetic form of adrenal hyperplasia

Bilateral adrenocortical hyperplasias associated with ACTH-independent Cushing syndrome

Macronodular

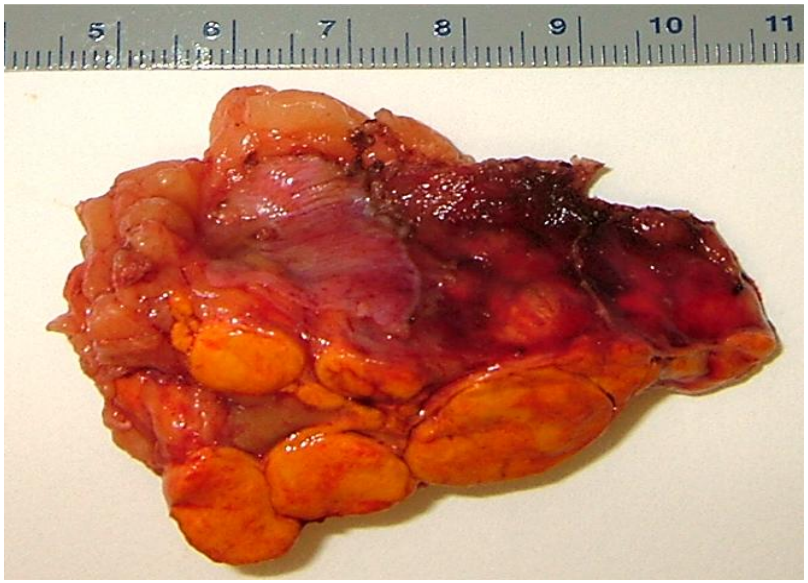
- → McCune-Albright syndrome, MEN1, FAP
- → MMAD, AIMAH PMAH
  - → Single large nodules and inter-nodular atrophy
  - → Multiple small and larger nodules and diffuse hyperplasia

Micronodular

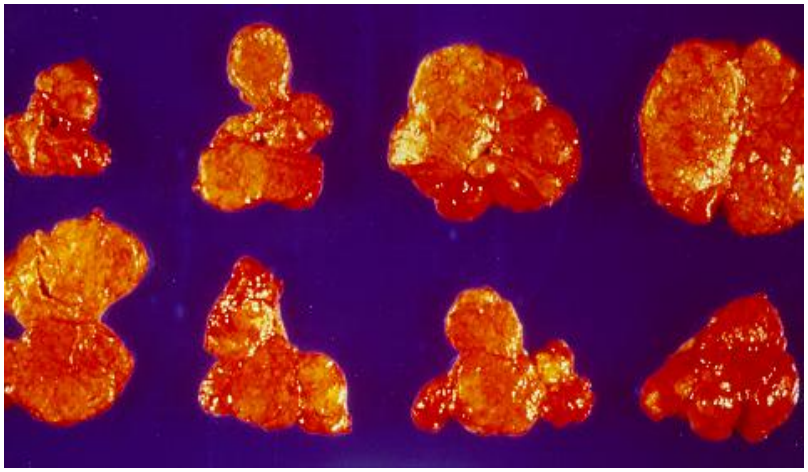
- → Pigmented
  - → •Isolated PPNAD
    •PPNAD with CNC
- → Non-pigmented
  - → •Isolated (iMAD)

MMAD/AIMAH/PMAH

Single large nodules
and inter-nodular atrophy →



Multiple small and
larger nodules and
diffuse hyperplasia →

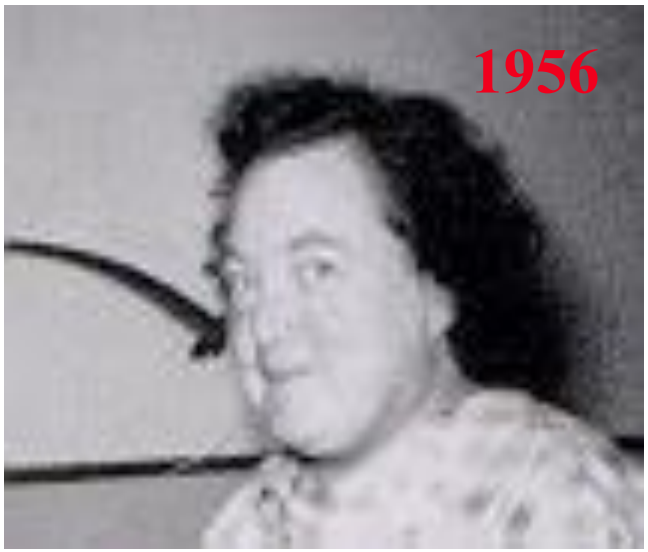



1939


1944


1949


1951


1956

Clinical and Genetic Heterogeneity, Overlap with Other Tumor Syndromes, and Atypical Glucocorticoid Hormone Secretion in Adrenocorticotropin-Independent Macronodular Adrenal Hyperplasia Compared with Other Adrenocortical Tumors

J Clin Endocrinol Metab, August 2009, 94(8):2930–2937

Hui-Pin Hsiao, Lawrence S. Kirschner, Isabelle Bourdeau, Margaret F. Keil, Sosipatros A. Boikos, Somya Verma, Audrey J. Robinson-White, Maria Nesterova, André Lacroix, and Constantine A. Stratakis

Section on Endocrinology and Genetics (H.-P.H., S.A.B., S.V., A.J.R.-W., M.N., C.A.S.), Program on Developmental Endocrinology and Genetics and Pediatric Endocrinology Interinstitute Training Program (M.F.K., S.V., C.A.S.), National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 20892; Division of Endocrinology, Diabetes, and Metabolism (L.S.K.), Department of Internal Medicine, Ohio State University, Columbus, Ohio 43210; Endocrinology Division (I.B., A.L.), Department of Medicine, Centre Hospitalier de l'Université de Montréal, Montréal, Québec, Canada H2W 1T8; and Department of Pediatrics (H.-P.H.), Kaohsiung Municipal Hsiao-Kang Hospital and Department of Pediatrics, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung 807, Taiwan

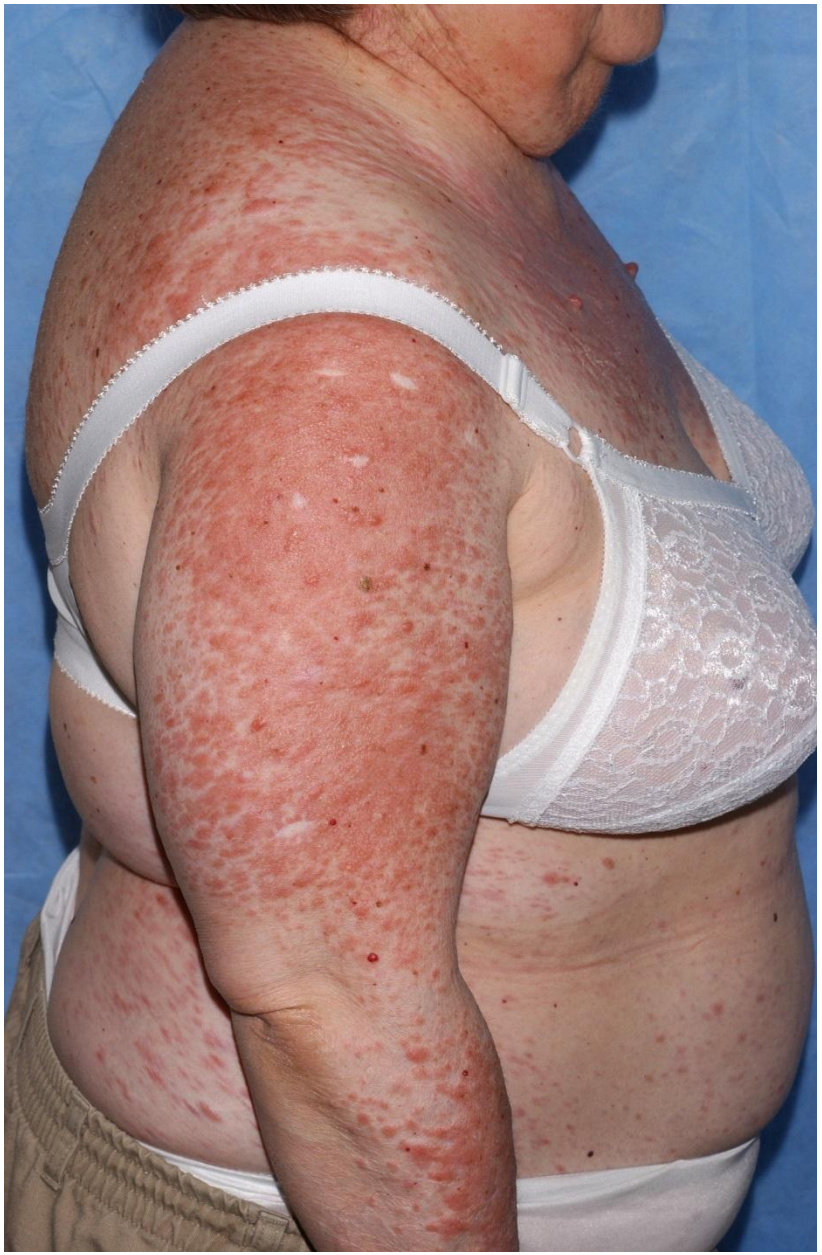
	Familial cases	Mutation	Other tumors (number of cases)	Other tumors in family members (number)
AIMAH (n = 16)	3	*MEN1* (Pro494Leu) *FH* (c.781del7) *APC* (c. 4393_4394delAG) *GNAS* (Arg201His), somatic	Thyroid adenoma (1) Lymphoma (1) Uterine fibroids (5) Parotid tumor (3) Parathyroid adenoma (1)	Thyroid cancer (1) in M Prostate cancer (1) in F Lung cancer (1) in M
ACS (n = 15)	None	None	Parathyroid adenoma (1) Nodular goiter (1)	None
APA (n = 19)	None	None	Thyroid nodule (1)	None
SCA (n = 32)	None	None	Thyroid nodule (1) Parathyroid adenoma (1)	Pancreatic Ca (F, GF on maternal side) Uterine Ca (M) Cervical Ca (S) Breast Ca (A) Pituitary tumor (F)

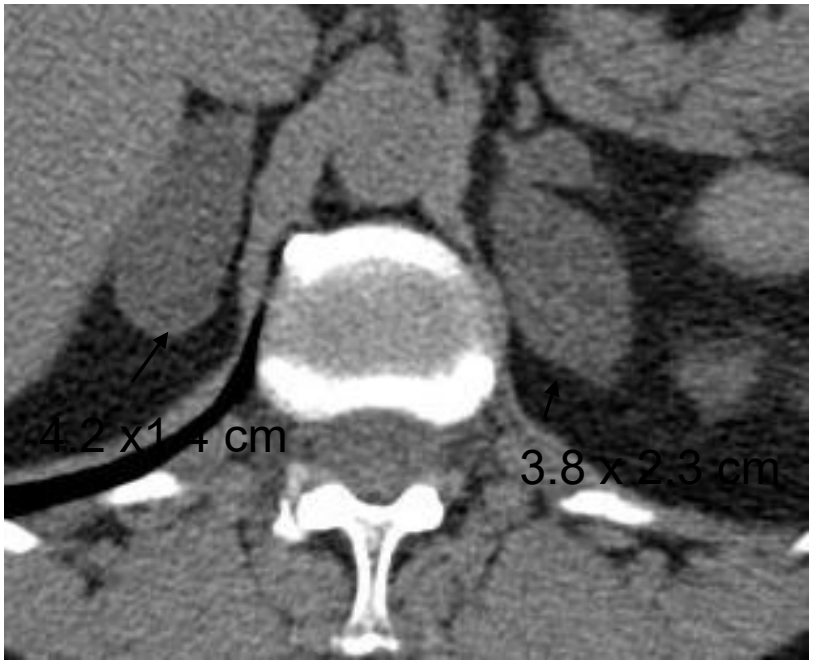
M, Mother; F, father; GF, grandfather; S, sister; A, aunt.

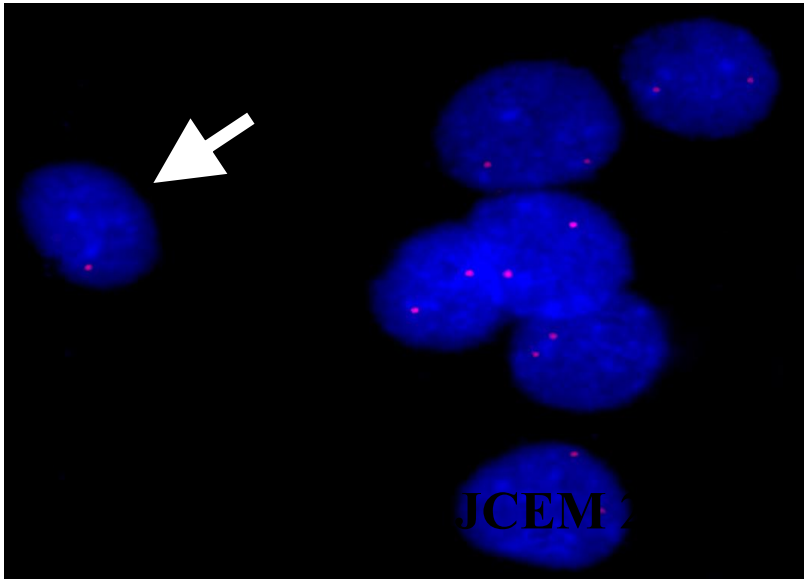
Macronodular hyperplasia in the context of a tumor syndrome

- Typically clinically silent adrenal masses that are detected incidentally with imaging studies conductedas part of the inevstigation of MEN1, APC, HLRCC, other
- Risk for cancer higher; occasionally functional, mostly subclinical CS

MMAD in HLRCC syndrome: associated with FH mutation

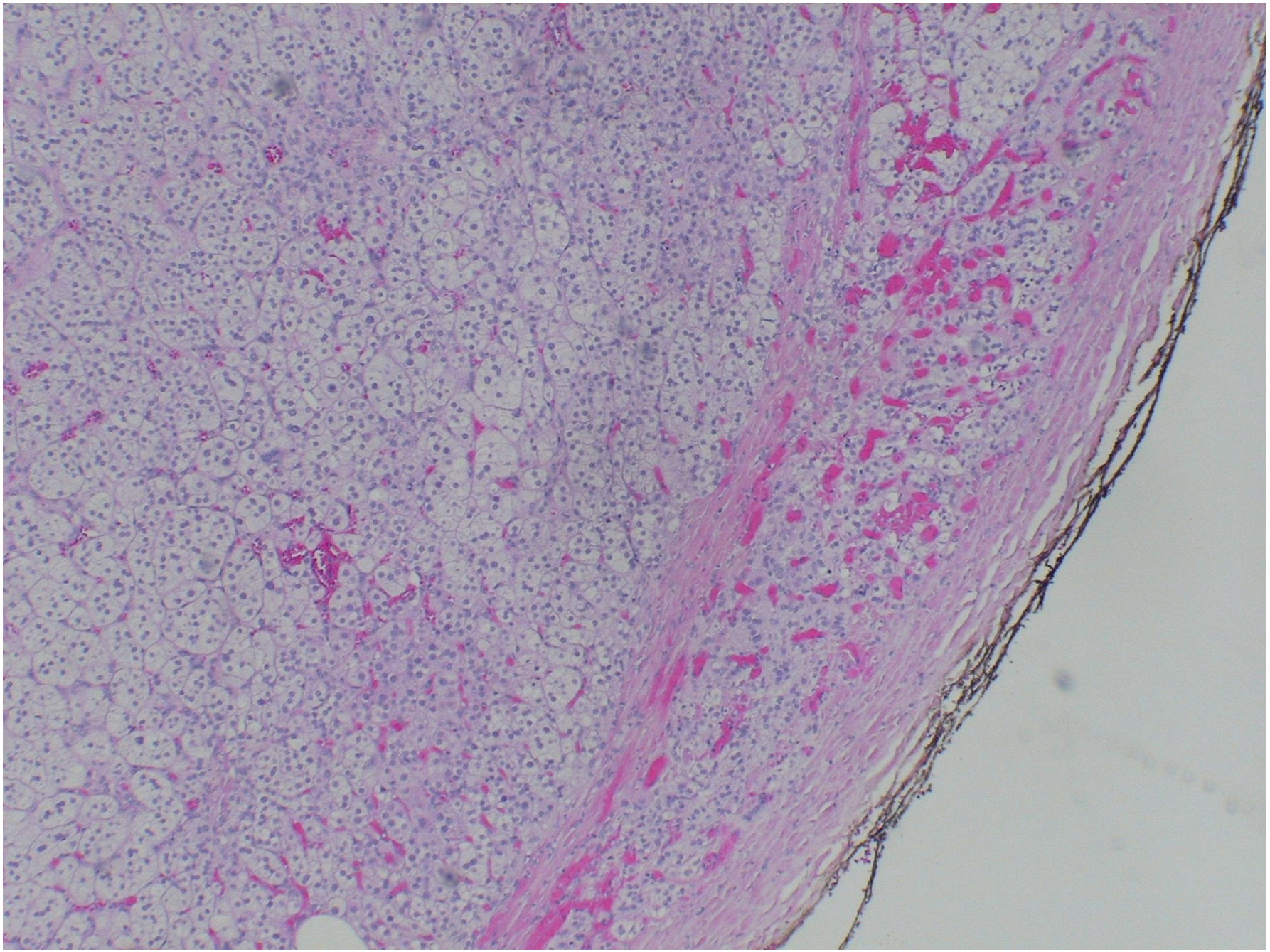


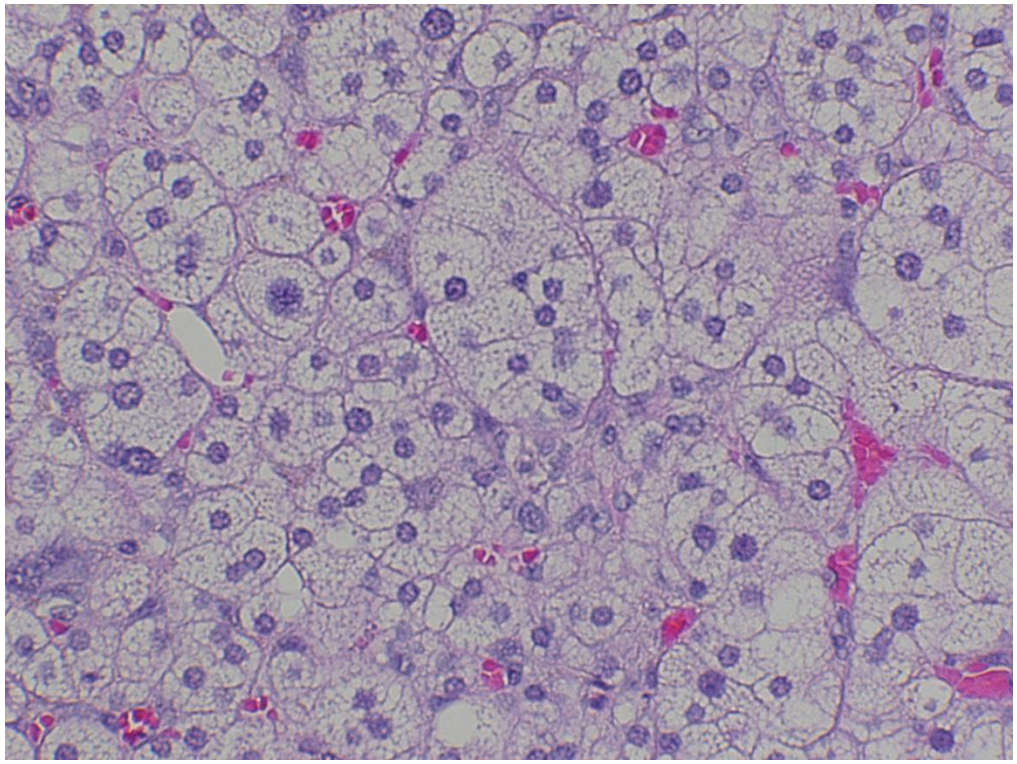


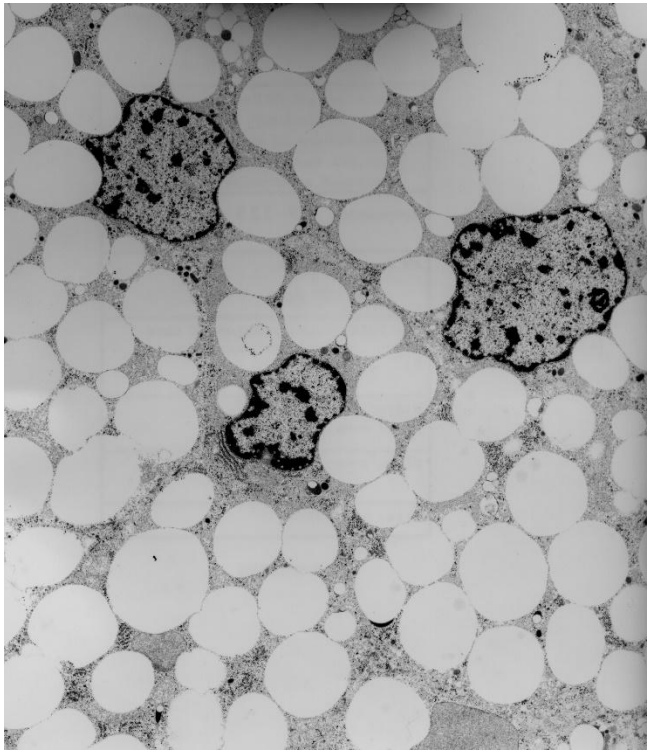


FH Mutation

- A germline mutation in the FH gene was found. It consisted of a 7-base pair deletion at nucleotides 782-788 and led to a premature stop codon at position 261 of the protein.
- The mutation segregated with the disease in the family







The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

ARMC5 Mutations in Macronodular Adrenal Hyperplasia with Cushing's Syndrome

Guillaume Assié, M.D., Ph.D., Rossella Libé, M.D., Stéphanie Espiard, M.D., Marthe Rizk-Rabin, Ph.D., Anne Guimier, M.D., Windy Luscap, M.Sc., Olivia Barreau, M.D., Lucile Lefèvre, M.Sc., Mathilde Sibony, M.D., Laurence Guignat, M.D., Stéphanie Rodriguez, M.Sc., Karine Perlemoine, B.S., Fernande René-Corail, B.S., Franck Letourneur, Ph.D., Bilal Trabulsi, M.D., Alix Poussier, M.D., Nathalie Chabbert-Buffet, M.D., Ph.D., Françoise Borson-Chazot, M.D., Ph.D., Lionel Groussin, M.D., Ph.D., Xavier Bertagna, M.D., Constantine A. Stratakis, M.D., Ph.D., Bruno Ragazzon, Ph.D., and Jérôme Bertherat, M.D., Ph.D.

ABSTRACT

BACKGROUND

Corticotropin-independent macronodular adrenal hyperplasia may be an incidental finding or it may be identified during evaluation for Cushing's syndrome. Reports of familial cases and the involvement of both adrenal glands suggest a genetic origin of this condition.

METHODS

We genotyped blood and tumor DNA obtained from 33 patients with corticotropin-independent macronodular adrenal hyperplasia (12 men and 21 women who were 30 to 73 years of age), using single-nucleotide polymorphism arrays, microsatellite markers, and whole-genome and Sanger sequencing. The effects of armadillo repeat containing 5 (*ARMC5*) inactivation and overexpression were tested in cell-culture models.

RESULTS

The most frequent somatic chromosome alteration was loss of heterozygosity at 16p (in 8 of 33 patients for whom data were available [24%]). The most frequent mutation identified by means of whole-genome sequencing was in *ARMC5*, located at 16p11.2. *ARMC5* mutations were detected in tumors obtained from 18 of 33 patients (55%). In all cases, both alleles of *ARMC5* carried mutations: one germline and the other somatic. In 4 patients with a germline *ARMC5* mutation, different nodules from the affected adrenals harbored different secondary *ARMC5* alterations. Transcriptome-based classification of corticotropin-independent macronodular adrenal hyperplasia indicated that *ARMC5* mutations influenced gene expression, since all cases with mutations clustered together. *ARMC5* inactivation decreased steroidogenesis in vitro, and its overexpression altered cell survival.

CONCLUSIONS

Some cases of corticotropin-independent macronodular adrenal hyperplasia appear to be genetic, most often with inactivating mutations of *ARMC5*, a putative tumor-suppressor gene. Genetic testing for this condition, which often has a long and insidious prediagnostic course, might result in earlier identification and better management. (Funded by Agence Nationale de la Recherche and others.)

From INSERM Unité 1016, Centre National de la Recherche Scientifique Unité Mixte de Recherche 8104, Institut Cochin (G.A., R.L., S.E., M.R.-R., A.G., W.L., O.B., L.L., S.R., K.P., F.R.-C., F.L., L. Groussin, X.B., B.R., J.B.), Faculté de Médecine Paris Descartes, Université Paris Descartes, Sorbonne Paris Cité (G.A., S.E., A.G., O.B., L.L., M.S., K.P., F.R.-C., L. Groussin, X.B., J.B.), Department of Endocrinology, Referral Center for Rare Adrenal Diseases (G.A., R.L., O.B., L. Guignat, L. Groussin, X.B., J.B.), and Department of Pathology (M.S.), Assistance Publique–Hôpitaux de Paris, Hôpital Cochin, and Unit of Endocrinology, Department of Obstetrics and Gynecology, Hôpital Tenon (N.C.-B.) — all in Paris; Unit of Endocrinology, Centre Hospitalier du Centre Bretagne, Site de Kério, Noyal-Pontivy (B.T.), Unit of Endocrinology, Hôtel Dieu du Creusot, Le Creusot (A.P.), and Department of Endocrinology Lyon-Est, Groupement Hospitalier Est, Bron (F.B.-C.) — all in France; and the Section on Endocrinology and Genetics, Program on Developmental Endocrinology and Genetics and the Pediatric Endocrinology Inter-Institute Training Program, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD (C.A.S.). Address reprint requests to Dr. Bertherat at Service des Maladies Endocriniennes et Métaboliques, Centre de Référence des Maladies Rares de la Surrénale, Hôpital Cochin, 27 rue du Faubourg St. Jacques, 75014 Paris, France, or at jerome.bertherat@cch.aphp.fr.

Drs. Assié, Libé, Espiard, Rizk-Rabin, Ragazzon, and Bertherat contributed equally to this article.

N Engl J Med 2013;369:2105-14.
DOI: 10.1056/NEJMoa1304603

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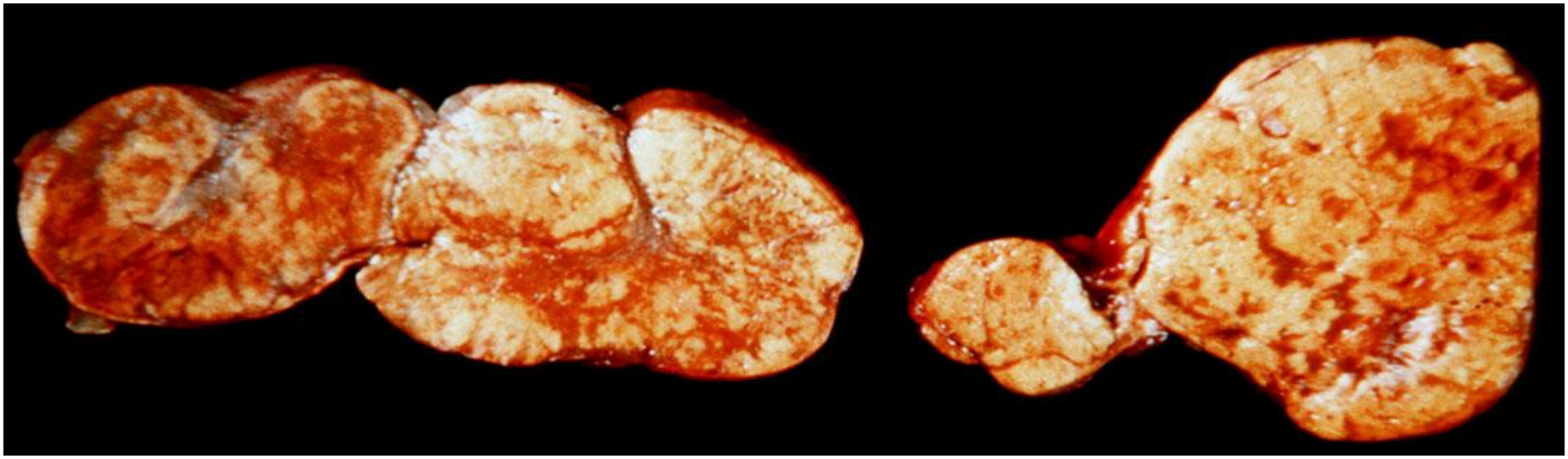
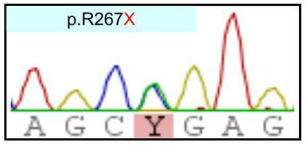
MMAD/ AIMAH/ PMAH: gene: *ARMC5*

N Engl J Med 369;22;Nov. 28, 2013

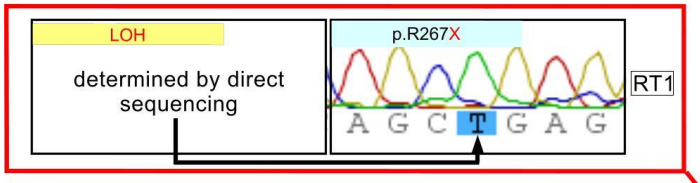
Armadillo Repeat Containing 5 (*ARMC5*)

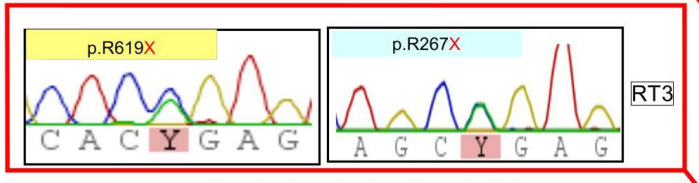


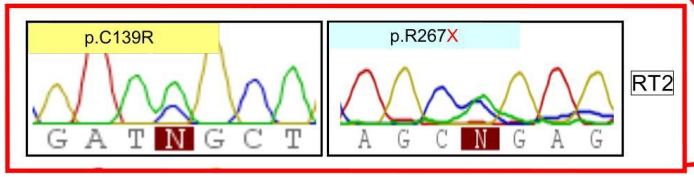
Germline DNA

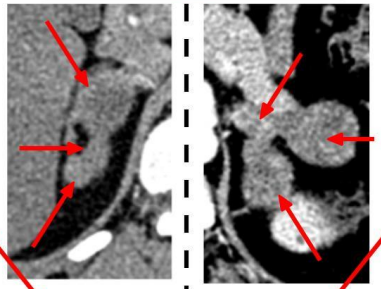


Tumor DNA





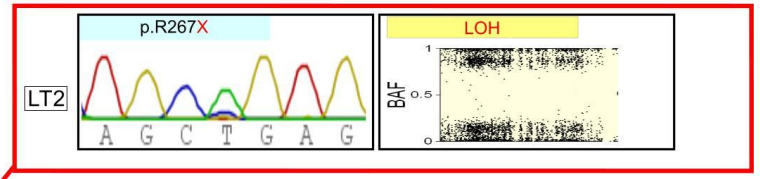


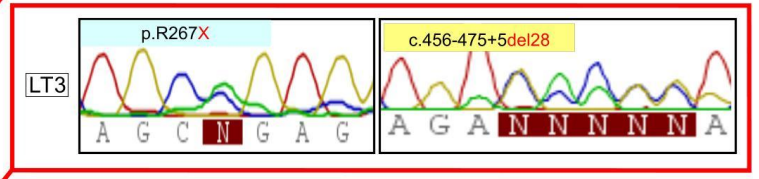


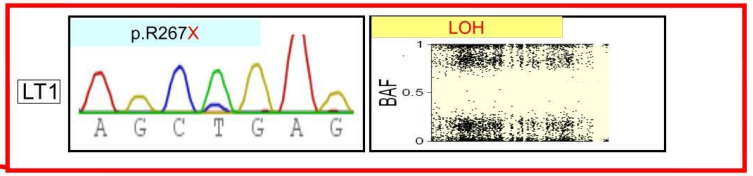
Right adrenal

Left adrenal

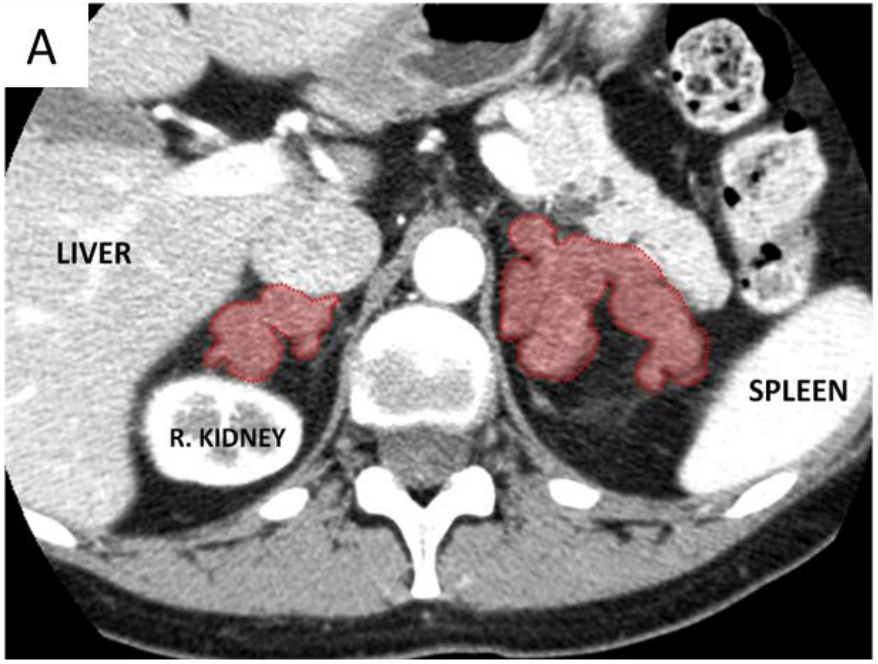
Tumor DNA

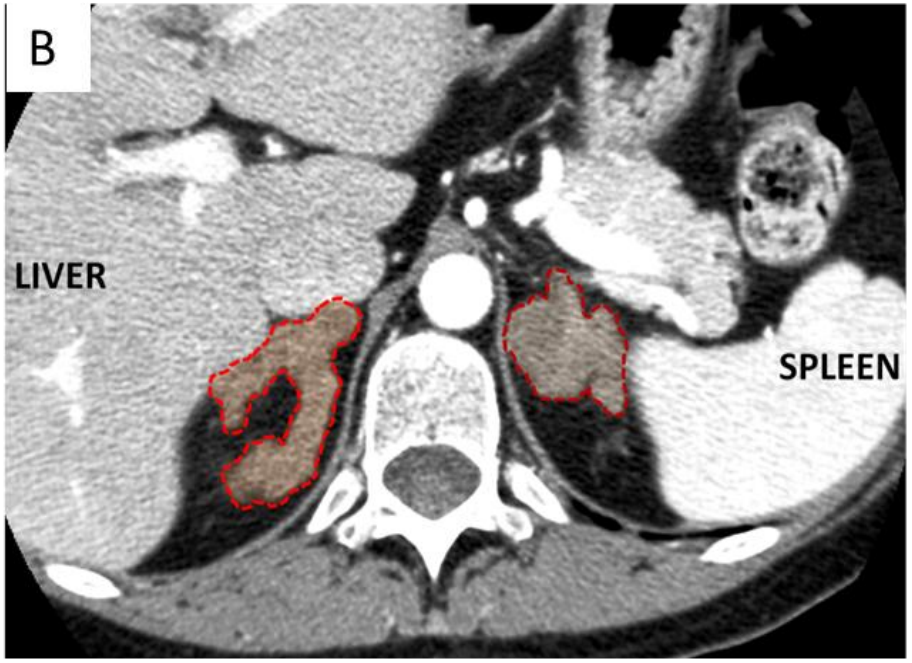


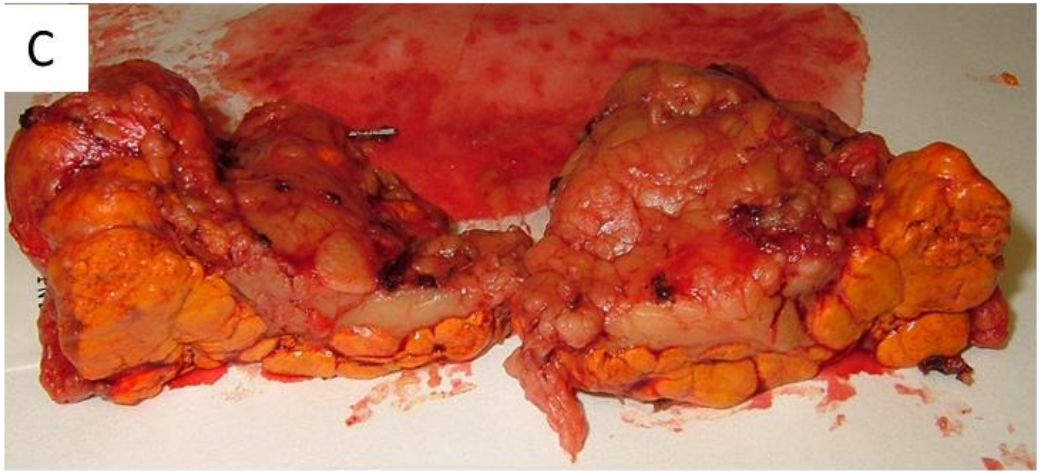


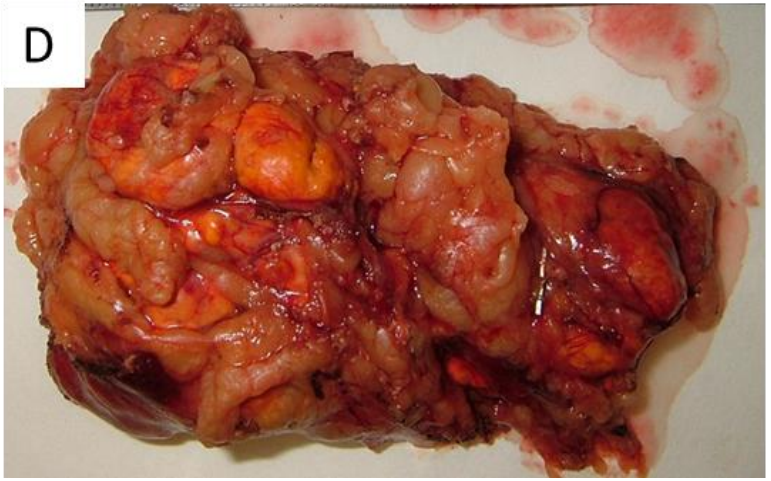


Correa et al. (2015): ARMC5 gene shows extreme genetic variance



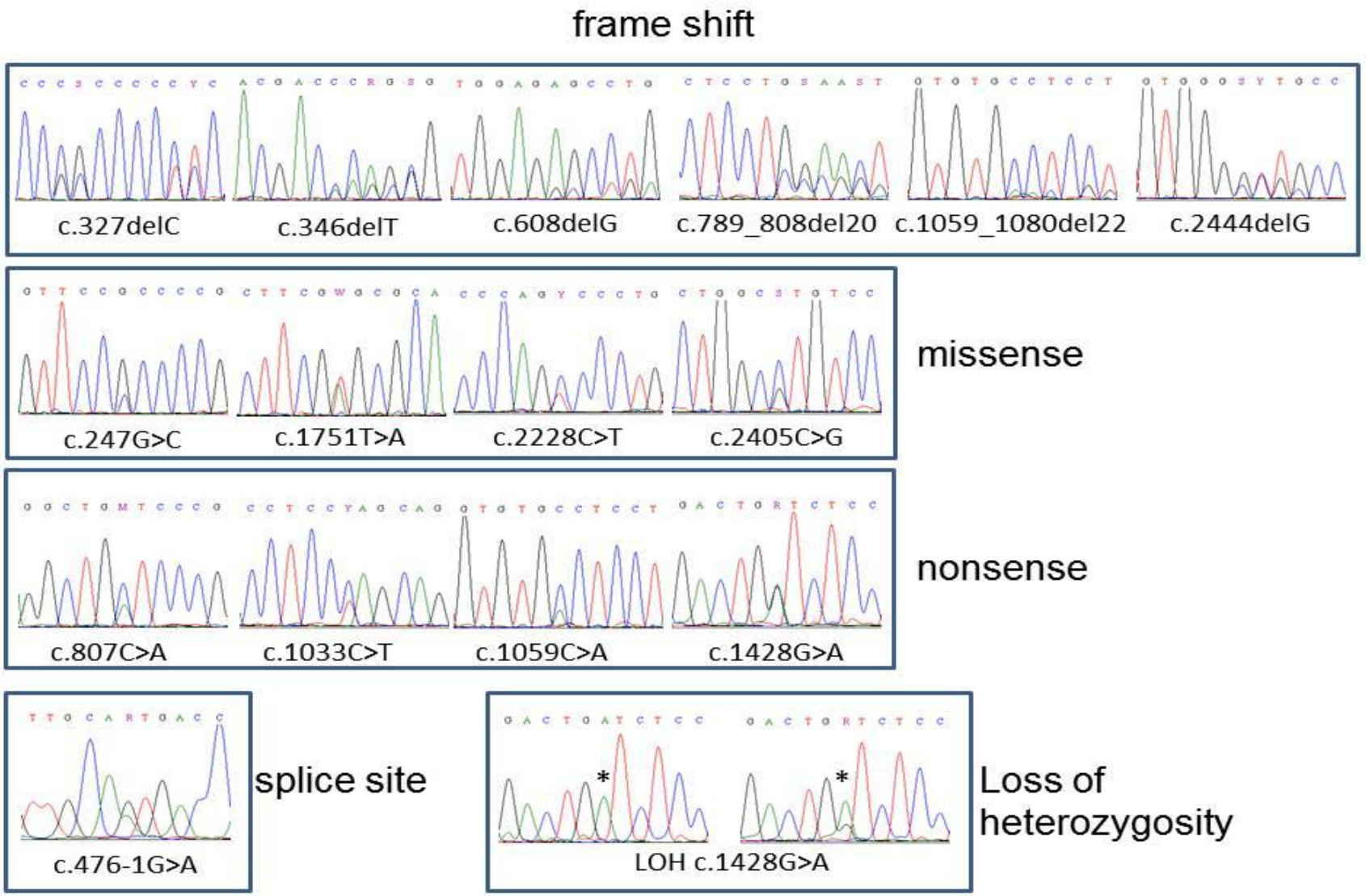






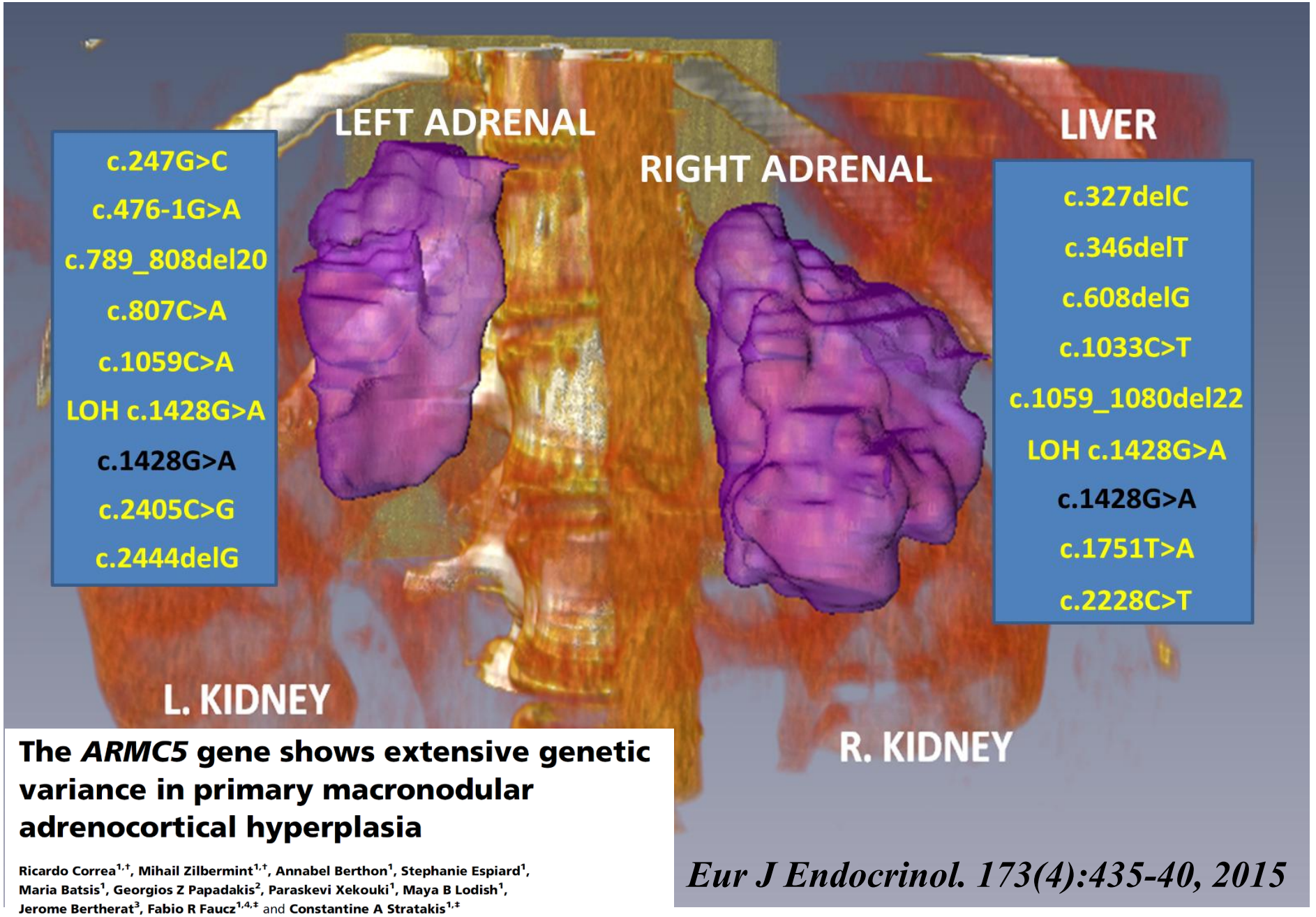
Correa et al. Eur J Endocrinol. 173(4):435-40, 2015

The *ARMC5* gene shows extreme genetic variance: each nodule with a "private" second hit



Correa et al. Eur J Endocrinol. 173(4):435-40, 2015

ARMC5 gene shows extreme genetic variance



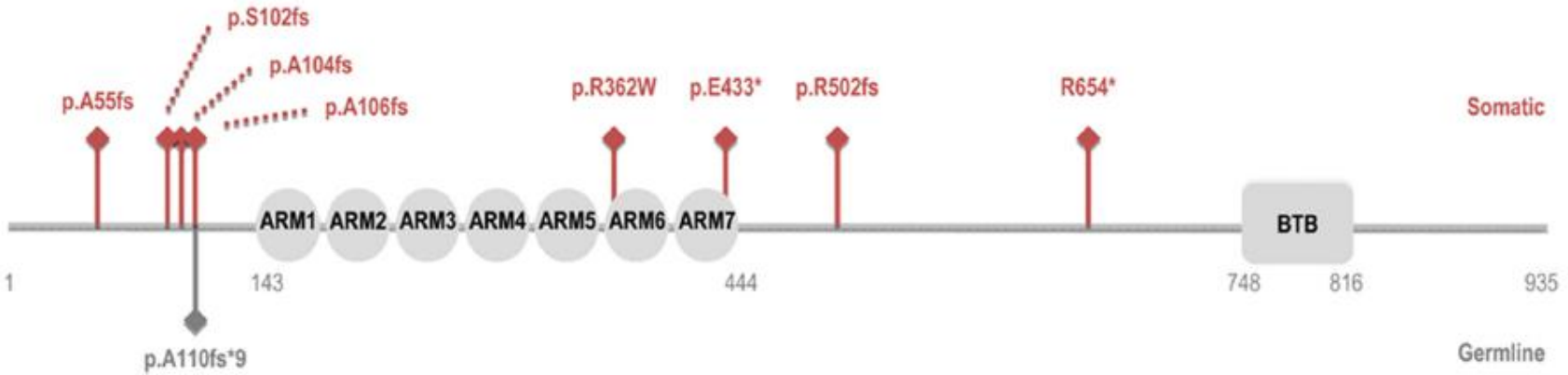
The *ARMC5* gene shows extensive genetic variance in primary macronodular adrenocortical hyperplasia

Ricardo Correa[1,†], Mihail Zilbermint[1,†], Annabel Berthon[1], Stephanie Espiard[1], Maria Batsis[1], Georgios Z Papadakis[2], Paraskevi Xekouki[1], Maya B Lodish[1], Jerome Bertherat[3], Fabio R Faucz[1,4,‡] and Constantine A Stratakis[1,‡]

Eur J Endocrinol. 173(4):435-40, 2015

Molecular and Clinical Evidence for an *ARMC5* Tumor Syndrome: Concurrent Inactivating Germline and Somatic Mutations Are Associated With Both Primary Macronodular Adrenal Hyperplasia and Meningioma

Ulf Elbelt,* Alessia Trovato, Michael Kloth, Enno Gentz, Reinhard Finke, Joachim Spranger, David Galas, Susanne Weber, Cristina Wolf, Katharina König, Wiebke Arlt, Reinhard Büttner, Patrick May,* Bruno Allolio,* and Jochen G. Schneider*

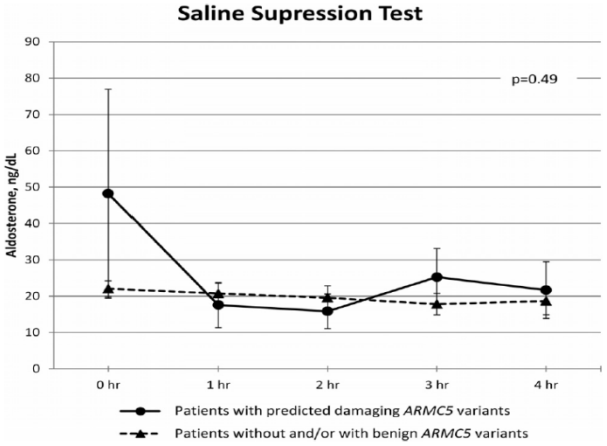


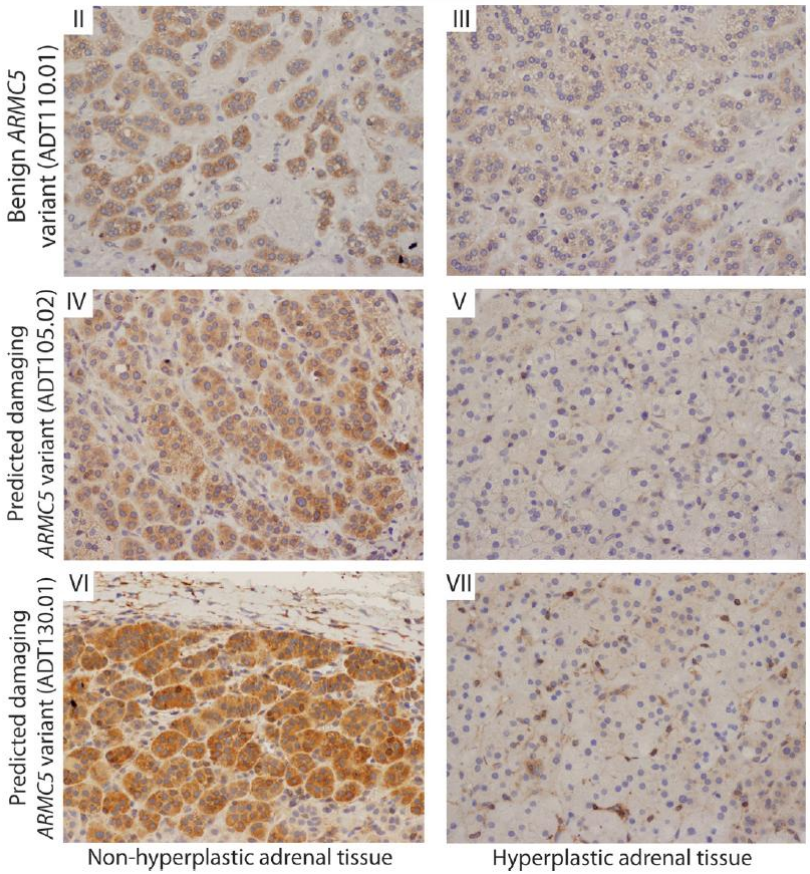
J Clin Endocrinol Metab, January 2015, 100(1):E119–E128

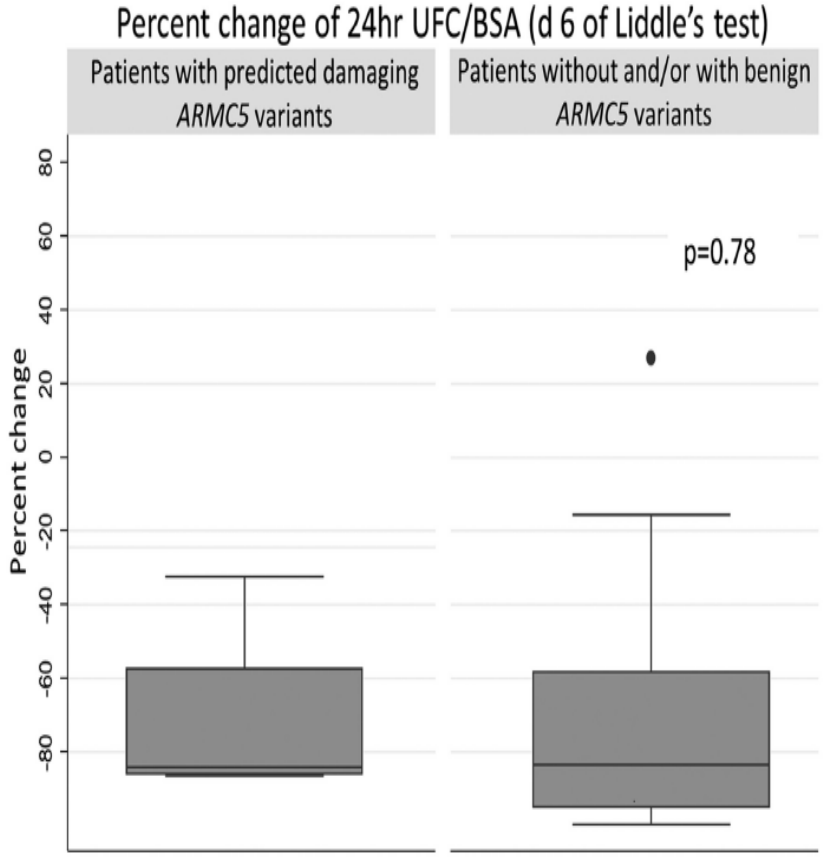
Primary Aldosteronism and *ARMC5* Variants

J Clin Endocrinol Metab, June 2015, 100(6):E900–E909

Mihail Zilbermint,* Paraskevi Xekouki,* Fabio R. Faucz,* Annabel Berthon, Alexandra Gkourogianni, Marie Helene Schernthaner-Reiter, Maria Batsis, Ninet Sinaii, Martha M. Quezado, Maria Merino, Aaron Hodes, Smita B. Abraham, Rossella Libé, Guillaume Assié, Stéphanie Espiard, Ludivine Drougat, Bruno Ragazzon, Adam Davis, Samson Y. Gebreab, Ryan Neff, Electron Kebebew, Jérôme Bertherat,* Maya B. Lodish,* and Constantine A. Stratakis*







Conclusions:

- Genetic studies in isolated MMAD/PMAH identified a gene, ARMC5 that explains half of the cases

- Food-dependent CS is not explained by *ARMC5* mutations

- It is not unusual to have combined aldosterone overproduction

- *ARMC5* may be involved in primary hyperaldosteronism

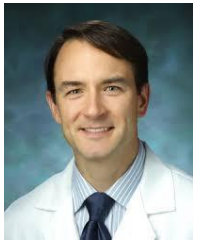
- Some of the affected adrenals produce ACTH, adding to the complexity of the work up

- *ARMC5* mutations carriers: often asymptomatic !

Crystal Kamilaris

Fady Hannah -Shmouni

Misha Zilbermint (now at JHU)

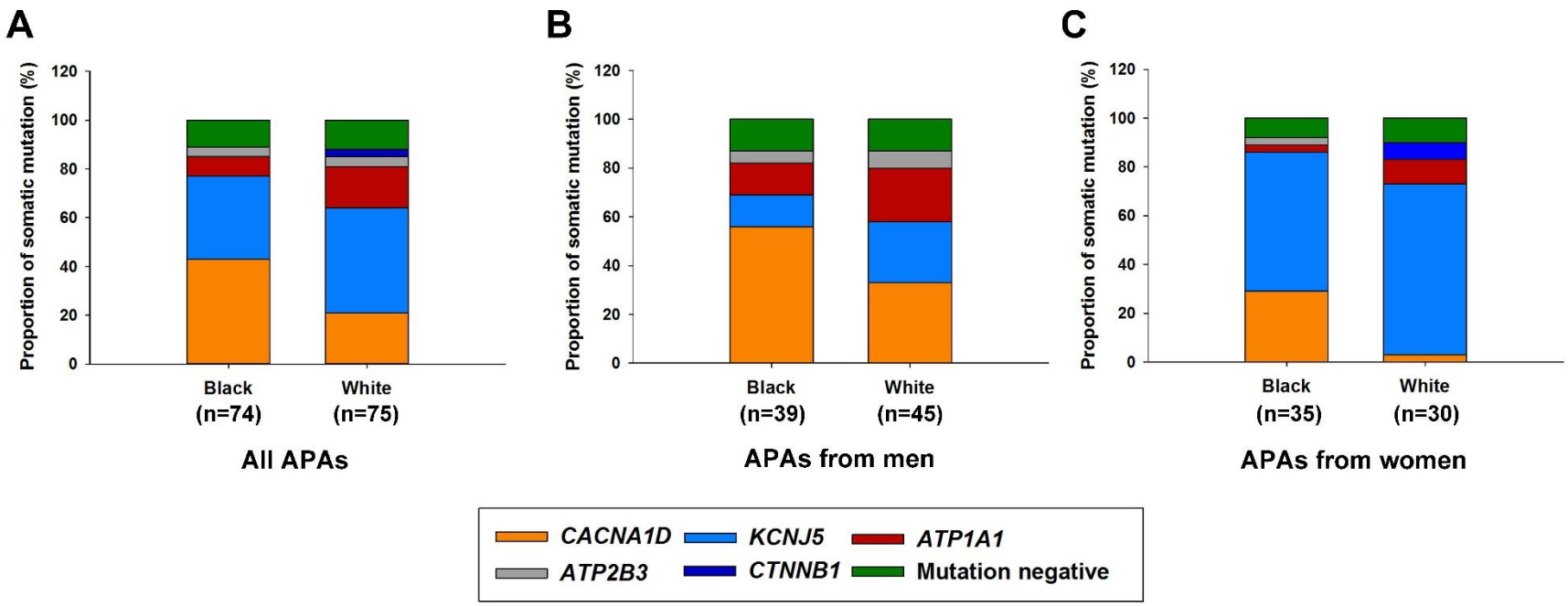


Andrew Demidowich (now at JHU)

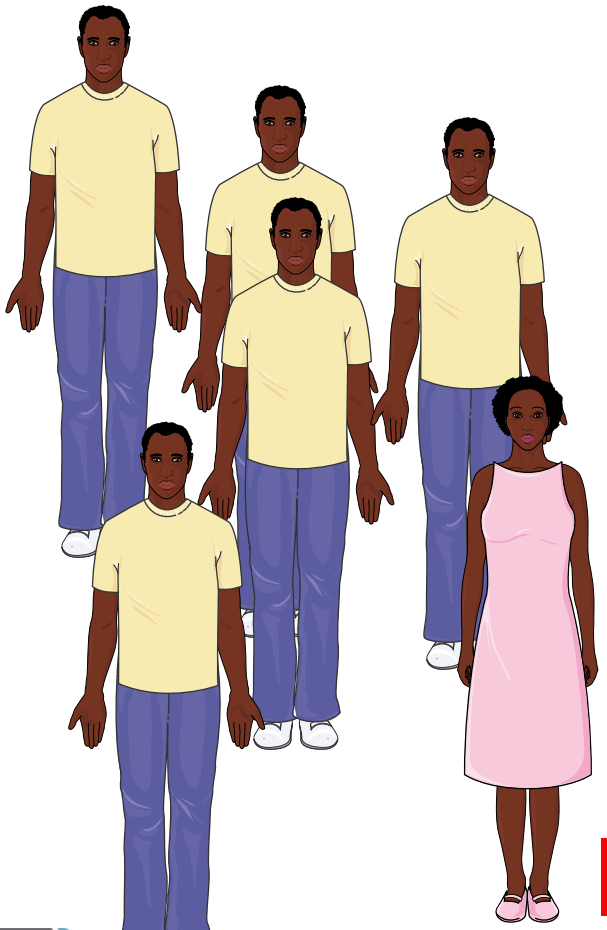
Genetic Characteristics of Aldosterone-Producing Adenomas in Blacks

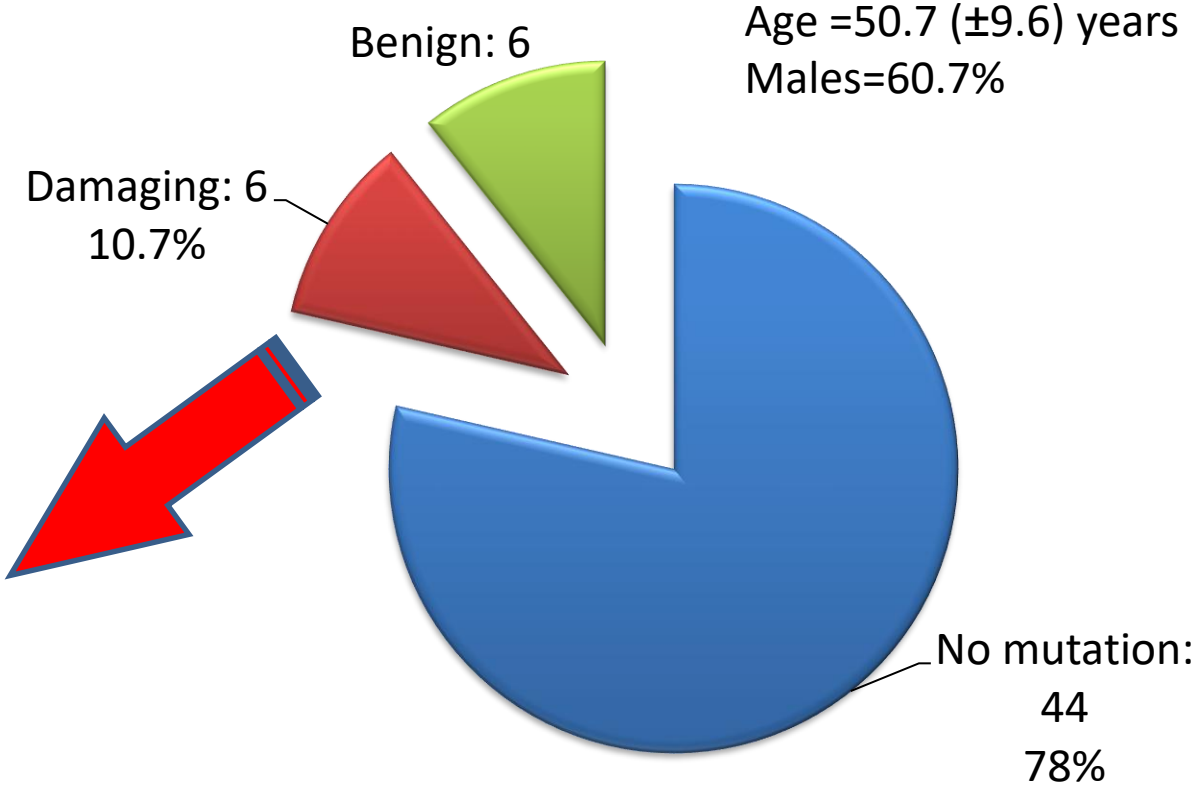
Kazutaka Nanba, Kei Omata, Celso E. Gomez-Sanchez, Constantine A. Stratakis, Andrew P. Demidowich, Mari Suzuki, Lester D. R. Thompson, Debbie L. Cohen, James M. Luther, Lan Gellert, Anand Vaidya, Justine A. Barletta, Tobias Else, Thomas J. Giordano, Scott A. Tomlins, William E. Rainey

Hypertension. 2019 Apr;73(4):885-892


A
B
C
Proportion of somatic mutation (%)
120
100
80
60
40
20
0
Black
(n=74)
White
(n=75)
All APAs
Black
(n=39)
White
(n=45)
APAs from men
Black
(n=35)
White
(n=30)
APAs from women
CACNA1D
KCNJ5
ATP1A1
ATP2B3
CTNNB1
Mutation negative

Results: *ARMC5* mutations





*p=0.0023

ARMC5 gene in CAAPA African American individuals

- We looked at chr16 CAAPA reference dataset for SNPs in ARMC5 gene region 100 kb upstream and downstream (hg19 positions chr16:31369010-31578488).

- After removing multiallelic SNPs and applying Genotype quality and Depth filters (GQ 20 and DP 7) and keeping only African American individuals.

- We have, 446 individuals and 3791 SNPs in ARMC5 gene region.

SNP	hg19_POS	CHROM	ALLELE.FREQ	ALLELE.FREQ	P_HWE	Missingness rate
rs116201073	31477442	chr16	T:0.93722	C:0.0627803	1	0
rs9921490	31473376	chr16	G:0.860987	T:0.139013	0.232	0

- Summary for two interesting SNPs in ARMC5 gene region rs116201073, and rs9921490:

The Association of ARMC5 with the Renin-Angiotensin-Aldosterone System, Blood Pressure, and Glycemia in African Americans. Joseph JJ et al.. J Clin Endocrinol Metab. 2020 Aug 1;105(8):2625-33

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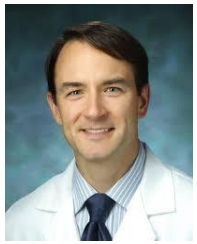

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